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Use of Microsurgery and Iloprost in the Infantile Arterial Injuries

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Background To evaluate the use and advantage of microsurgical intervention and intravenous iloprost administration in delayed infantile artery injuries.
Methods and Results Four patients were followed up and treated in our clinic between June 2003 and June 2006 for infantile artery injuries and distal ischemia. The average age of the 4 infants (3 girls, 1 boy) was 134.7± 33.6 days. The reason for all of the artery injuries was iatrogenic. Tissue necrosis started in patches in 2 babies who were admitted at the 12th hour after ischemia (19th and 22nd hours), and therefore the artery was repaired by microsurgery. Iloprost infusion was also used in addition to the conservative treatments. The other 2 patients were assessed before the first 12 h after distal ischemia and were treated by iloprost without any surgical intervention. None of the patients lost any tissue or extremities during the 9 months (average) follow-up time. One of our patients died following the ventricular septal defect repair at the 9th month after a successful repair of artery.
Discussion We believe that intravenous iloprost infusion is very effective in the treatment of distal ischemia when used in addition to the conservative treatment methods for artery injuries in infants. (*Circ J* 2007; **71:** 554–558)

Key Words: Acute; Iloprost; Microsurgery; Neonatale vascular injury

Although not very frequent in infants, vascular injury is a pathology that can severely threaten the life of the patients or their extremities as a result of the narrowness of their vessel diameter. Vascular injury rate in infants is below 1% according to a multi-centered research[1] Similarly, nearly all of the artery injuries during the first and second years are of iatrogenic origin[1,2] Conventional medical treatment methods used after arterial injuries during neonatal and infantile periods include the use of heparin, thrombolytic infusions and treatments such as surgical embolectomy, which can be carried out when necessary[3–7] Despite conservative treatments, if the spasm in the arterial cannulation cannot be relaxed, in some patients extremity ischemia may continue and surgery becomes inevitable.

Iloprost is a stable prostacyclin analogue with a long-term effect[8] Prostacyclin is a molecule composed of endothelial cells through cyclooxygenase. Prostacyclin inhibits platelet aggregation, leukocyte adhesion, chemotaxis and superoxide-anion production[9] Moreover, prostacyclin is a potent vasodilator[10] It is also proven to be effective in inhibiting the changes in the endothelial microvascular permeability occurring as a result of ischemia–reperfusion[11,12]

In the current study, we used an intravenous infusion of iloprost in addition to the conservative medical treatment to benefit from the effects mentioned above with respect to severe ischemia of lower extremity caused by artery injury in the infantile period (especially in 6 months). Our aim is to discuss the use of iloprost in addition to the conservative treatment and artery repair in arterial injuries during the infantile period with microsurgical methods.

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Methods

Four infants were treated in our clinic between June 2003 and June 2006 for iatrogenic acute artery occlusion. Three of these patients developed ischemia in the related extremity because of the cardiac catheterization interventions carried out in the centers other than our University. The last patient's artery was replaced using a cut-down procedure during a ventricular septal defect (VSD) operation. All conservative treatment methods, including thrombolytic infusion, were applied to all of the patients, except for 1 patient who had cardiac surgery.

The protocol and conduct of this retrospective study was approved by our organizational review and ethics board.

The patients were followed up for 274.7±75.1 days in the postoperative period by physical examination and portable Doppler. Demographic data of the patients, diagnosis and treatment methods are summarized in Tables 1 and 2.

After the patients were admitted to our hospital, their vascular systems were examined in detail routinely using Doppler ultrasonography and a manual Doppler. In patients with severe delayed ischemia in extremities despite heparinization (18 units·kg^{-1}·h^{-1}), thrombolytic therapy (tPA, 0.5 mg·kg^{-1}·h^{-1}), arterial repair and embolectomy was carried out using an emergency microsurgical method. Conservative treatment methods contain heparin infusion (18 IU·kg^{-1}·h^{-1}), thrombolytic therapy (0.5 mg·kg^{-1}·h^{-1}), arterial repair and embolectomy. Heparin infusion was administered as an intravenous infusion at a dose of 18 IU·kg^{-1}·h^{-1}. tPA (Actylyse®) was administered as an intravenous infusion at a dose of 0.5 mg·kg^{-1}·h^{-1}. The vascular anastomosis was carried out with a loop under 2.5 magnifi-

Table 1 Demographic Data of All Patients

	Age (day)	Weight (g)	Follow up (day)	Lenght (cm)	Etiology
1st patient	94	4,100	275	55	Iatrogenic (cardiac catheterization)
2nd patient	153	6,200	368	61	Iatrogenic (cardiac catheterization)
3rd patient	122	5,400	272	59	Iatrogenic (arterial cut-down)
4th patient	170	6,700	184	63	Iatrogenic (cardiac catheterization)

Table 2 Clinical Progress and the Treatment Given to All Patients

	Symptoms	Diagnostic method	Treatment method
1st patient	Cold, pale extremity without pulse, bruises under the knees	Doppler ultrasonography (at 22nd h)	Conservative medical (included thrombolytic) + microsurgery (saphenous vein interposition) + iloprost infusion (postoperative 7 days)
2nd patient	Cold, pale extremity without pulse, skin necrosis under groin that might turn into gangrene	Doppler ultrasonography (at 19th h)	Conservative medical (included thrombolytic) + microsurgery (end-to-end anastomosis) + iloprost infusion (postoperative 7 days)
3rd patient	Coldness, paleness under groin, no pulse. Bruises in patches under the ankle	By Doppler ultrasonography at 26th h following the closure of VSD via open heart surgery	Arterial catheterization + heparin infusion + iloprost infusion (7 days)
4th patient	Cold and pale extremity without pulse, capillary filling decreased but existent	No flow in iliac artery in Doppler ultrasonography. Pulsatile flow detected in popliteal artery at 48th h following the medical treatment	Heparin infusion + thrombolytic infusion + iloprost infusion (7 days)

VSD, ventricular septal defect.

cation. Following the surgical intervention, iloprost treatment was added to the conservative treatment. Iloprost treatment was started at a dose of $0.5\,ng\cdot kg^{-1}\cdot min^{-1}$ and was titrated up to maximum tolerable dose. The maximum dose did not exceed $2\,ng\cdot kg^{-1}\cdot min^{-1}$. Iloprost was administrated to the patient 16 h a day and this treatment was continued for 7 days. Iloprost was added to the treatment of 2 patients who could not be operated on but was being treated by conservative treatment methods. Patients' vascular systems were followed up daily using a manual Doppler and unless a difference was detected in the vascular system during the routine follow-up, the patients were checked weekly with Doppler ultrasonography. The patients were also closely followed up after they had been discharged.

None of the patients underwent an angiography for ethical reasons as there was no medical need during the postoperative period.

Results

Our 1st and 2nd cases were the patients, in whom a conservative treatment was already started when ischemia in the extremities and angiographies were detected at another center. These patients were referred to our clinic, when their clinical conditions became worse, despite the conservative treatment. Both of these patients had been diagnosed with VSD and pulmonary hypertension as cardiac pathology in catheter study. The 1st patient was admitted to our clinic at the 22nd hour after the angiography, with color changes of purple patches in the lower extremity and the extremity was severely pale and cold. No flow was detected in the iliac artery and distal in the Doppler ultrasonography of the patient. The patient was taken to emergency surgery and embolectomy was carried out without balloon inflation in the proximal and distal parts of the common femoral artery using a 2–3 Fr catheter. In both patients who were operated, the distal artery was irrigated with heparinized fluid. The common femoral artery, of which the composition was damaged within a segment of approximately 1.5 cm, was resected and saphenous vein taken from the groin of the same leg was interposed with 7/0 polydioxanone suture. Pulsatile pulse was detected in distal of saphenous vein. The patient was given a heparin infusion ($18\,units\cdot kg^{-1}\cdot h^{-1}$) and iloprost (Ilomedin®) infusion ($0.5\,ng\cdot kg^{-1}\cdot min^{-1}$) during the postoperative period.

As a result of the compartment syndrome, which occurred below the patient's knee at the 36th hour, medial and lateral fasciotomy was applied. The patient with no clinical problems was discharged on the 19th day after the operation. The patient, whose vascular system was followed up for 9 months postoperatively, was operated for VSD. At the 68th hour after the VSD operation, the patient died because of pulmonary hypertensive crisis.

In our second case, ischemia in the related extremity was diagnosed at another clinic by angiography. After conservative treatment in another clinic, the patient was referred to our clinic when his clinical condition deteriorated. In the Doppler ultrasonography, we found that there was no arterial flow in the common and distal femoral artery. The lower part of the extremity, starting from the groin was cold and pale and seemed purple in patches with a possibility of developing gangrene (Fig 1). The patient had a embolectomy and microsurgical intervention for artery injury urgently. The artery was damaged within a segment of 4 mm because of the multiple arterial punctures done for cardiac catheterization, and an end-to-end anastomosis with 7/0 polydioxanone suture was carried out. During the postoperative period, heparin ($18\,units\cdot kg^{-1}\cdot h^{-1}$) and iloprost infusion (an average of $1\,ng\cdot kg^{-1}\cdot min^{-1}$) were administered 16 h a day for 7 days. On postoperative day 8, the patient whose necrotic areas in the skin were healed, was treated with open wound care in the lower extremity. On postoperative day



Fig 1. A 153-day-old girl baby 19 h after angiography intervention via left femoral artery.



Fig 2. This image shows left lower extremity on the postoperative day 24.



Fig 3. Twelfth month after femoral artery repair.

24, the patient, who had no other complaints than patchy skin hyperpigmentation, was discharged (Fig 2). In the first month following the discharge, the patient's VSD was repaired with open heart surgery. All peripheral pulses of the patient during his 12 months of follow-up were detectable by Doppler (Fig 3).

Arterial injury occurred in our third infant after the insertion of an arterial catheter using the cut-down method for VSD operation. The arterial catheter could not be placed percutaneously and therefore, was placed via cut-down. The patient did not display any ischemia during the first 24 h. At the 26th hour of the postoperative period following the VSD operation, coldness and paleness were detected and no pulse was detectable with Doppler during the examination of the artery. Therefore, the arterial cannula was removed and all conservative treatments, except thrombolytic treatment were carried out. Heparin infusion was administered as an intravenous infusion at a dose of 18 $IU \cdot kg^{-1} \cdot h^{-1}$. As the extremity arterial circulation was not supplied properly, an iloprost infusion was administered at the 30th hour. Iloprost infusion (an average of 1 $ng \cdot kg^{-1} \cdot min^{-1}$) was administered 16 h a day for 7 days. The related extremity got warmer in the first 6 h of the treatment. Pulsatile flow was detected in the popliteal artery with Doppler at the 8th hour following the treatment. Doppler ultrasonography performed on the 4th day in the postoperative period showed that the peripheral circulation was normal. This patient is now within the 9th month of the postoperative period and peripheral pulses are still detectable by Doppler.

The 4th patient was referred to our clinic with a lower extremity ischemia, which had occurred after a cardiac catheterization at a different clinic. This patient was diagnosed during the catheter procedure, with complete type atrioventricular canal defect. The patient, whose extremity ischemia did not improve despite conservative treatment conducted at the other clinic, was referred to our clinic at the 9th hour after the angiography. The Doppler ultrasonography did not display any flow in the iliac artery or the distal portions. As the ischemia in the extremity did not worsen, no surgical intervention was carried out, and we decided to continue the current treatment with iloprost infusion and to monitor the patient. Iloprost infusion (an average of 1 $ng \cdot kg^{-1} \cdot min^{-1}$) was given 16 h a day for 7 days. At the 14th hour after the treatment, the patient's pulse could be manually palpated and the flow in the popliteal artery continued to be normal for 8 days after the treatment. The patient is in the 6th month following treatment and his vascular system is normal as shown by Doppler.

Discussion

Beside the cardiac catheterization and despite of the increasing number of infants who are monitored continuously with respect to their arterial pressure in the intensive care units, the number of arterial injuries has not increased significantly compared to the current adult population[3,13,14] Nevertheless, arterial occlusions during the neonatal and infantile period can result in catastrophic events[3,15–17]

Following the arterial catheterization, infants might exhibit distal ischemia[3] tissue necrosis[3] pseudoaneurysms[13] or localized bleedings[3] similar to adults. Moreover, infants might also encounter problems, such as discrepancies in growth and development in one of their extremities, unlike the adults[3,18] The most common cause of arterial injury in infants is iatrogenic[3] Iatrogenic artery injuries mostly include direct arterial punctures, diagnostic and therapeutic cardiac catheterization and incorrect intra-arterial injections.

In cases of arterial injury in infants, conservative methods (antispasmodics, heparin and thrombolytic drugs) are the common treatment methods used today. These treatment methods are likely to treat the distal ischemia caused

by arterial spasm after angiography. The treatment is carried out both by vascular dilatation and thrombus dissolution. However, in some cases, distal ischemia cannot be treated by medical treatment and even can deteriorate because of certain factors, such as increased number of arterial punctures or damage to vascular structure. In the current study, we carried out microsurgery on both of our patients, who had no arterial flow in the extremity as a result of delayed intervention indicated by severe ischemia and extensive skin necrosis in the related extremities. We added iloprost infusion to the conservative treatment in these patients, as well as in 2 other patients who were admitted within the first 12 h after ischemia and who did not have severe ischemia findings or necrosis on the effected extremities. Neither the first delayed cases (admission at the 19th–22nd hours) nor the second had any tissue loss. A complete remission was obtained in both of our cases. We also believe that iloprost infusion started in the postoperative period and continued for about 7 days in addition to microsurgery carried out on both of the patients admitted to our clinic at a very late hour of the hot ischemia, had a very important role in our success.

We primarily preferred iloprost infusion instead of surgical intervention on the other 2 patients whose ischemia in the related extremity did not improve despite of the conservative treatment because they were admitted to our clinic in the early phase of ischemia and the degree of ischemia was not severe. We think that the administration of iloprost infusion for 7 days is very beneficial in the recovery of arterial patency. Iloprost is a stable analogue of prostacyclin (prostaglandin I_2, PGI_2), which is an endogenous prostaglandin synthesized from arachidonic acid, primarily in the vascular endothelium. We believe that the positive effect of iloprost on distal ischemia originates from its direct effect of relieving the arterial vasospasm by vasodilatation![10] Moreover, it also might be helpful in regulating the prostacyclin levels which decrease because of the local damage in the endothelial cells on the site of arterial puncture. As a result of this indirect effect, we can prevent the increase in the production of the adhesion molecules[19] and the platelet and leukocyte activation related to prostacyclin production, which is decreased locally because of the endothelial damage![19] As a consequence of this latter benefit, localized thrombus development in the damaged artery lumen will be reduced.

Moreover, the administration of iloprost might also reduce the reperfusion damage that may occur after the delayed and surgically intervened distal ischemia cases as shown in our study group![9,12,20] Following the ischemia-reperfusion, an interstitial edema with polymorphonuclear (PMN) sequestration might occur in the related extremity and the ischemia may become more severe. Prostacyclin might reduce this tissue edema and swelling mediated by PMN;[21] and can prevent the extension of ischemia in the related extremity after the reperfusion. Iloprost prevents the increase in the distal ischemia after ischemia-reperfusion not only by decreasing platelet aggregation and vasodilatation;[22] but also by influencing PMN leukocytes by 3 mechanisms. These 3 mechanisms allow the decrease of PMN activation;[23] the decrease of PMN activity of migration to inflammation area and eventually by the inhibition of the adhesion of PMN to endothelial cells![24]

All arterial injuries treated in our clinic were followed up on the basis of the physical examination findings and Doppler examination. The diagnosis of ischemia in all of our patients were based on findings such as coldness, paleness, lack of pulsatile peripheral pulses and a delay in capillary filling. In cases with prolonged ischemia, iloprost infusion in addition to the conservative medical treatment convenient for the treatment of artery injuries carried out at the 9th hour or earlier may be sufficient. However, clinical examinations of the patients and the degree of the ischemia in the related extremities are the most important factors, which determine our decision for a surgery. After the surgery, an iloprost infusion will be very beneficial to minimize the extremity and tissue loss in similar patient groups. The patients with ischemia, whose condition did not improve or did get worse despite of all possible conservative treatment and iloprost administration, were referred to surgery. We administered an iloprost infusion to all our patients in addition to the conservative treatment methods applicable for distal ischemia. We think that iloprost is beneficial both for its strong vasodilatation in patients with distal ischemia, treated in the first 9th hour after the ischemia and for its helpful effects on ischemia-reperfusion. Under the light of this knowledge, we can say that iloprost is beneficial especially for the narrow arteries of infants and in microcapillary circulation in addition to its effect on larger vessels.

Consequently, we believe that iloprost as an additional treatment to conservative ones after the arterial injury in infants might be beneficial in early and late ischemia. As a result of its above mentioned benefits, iloprost can be used both in distal ischemia in patients who were treated with microsurgery and in infants treated only with drug administration. We think that iloprost is an important alternative to recover regular artery circulation and full arterial patency on ischemic tissue in infants.

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