Intravenous Infusion of Prostaglandin E1 Therapy in Extremity Ischemia

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Abstract
Prostaglandins are potent vasoactive agents with wide variety of other actions - vasodilatation, fibrinolysis and inhibition of platelet aggregation. PGE1 was the agent used since 1973 for cardiovascular diseases, mainly in patients with advanced PVD. PGE1 intra venous infusion has shown to be beneficial in limb threatening ischemia, especially when reconstructive procedures are not feasible and also as an adjunct when there is residual ischemia after revascularization. The review of literature and the use of PGE1 in CLI is presented here along with our experience in NIMS.

Keywords: Extremity ischemia, prostaglandin E1 therapy, prostaglandin infusion

Introduction
Prostaglandins (PGs) were discovered in 1935 as a blood-pressure-lowering substance from the prostate gland secretion. von Euler found that seminal fluid and seminal vesicles from most animals including men contain a substance which causes contraction of the smooth muscle of the uterus. He named this new substance as “prostaglandins” since they were originally thought to be secreted by the prostate gland. During those decades, scientists were unaware of how these substances were produced and how they functioned. It was only after 20 years that the mysteries covering the new substance PG were uncovered by three brilliant scientists. PG E₁ (PGE₁) was first isolated in 1957 by Bergström and Sjövall. They discovered the basic chemical structure to be unsaturated fatty acids with 20 carbon atoms where five are structured as a ring. In 1976, prostacyclin was discovered as a potent inhibitor of platelet function and as a strong vasodilator. Both PGE₁ and PG₁ are compounds of endogenous origin and spread out their activities by reacting through the same surface receptor. These pharmacological properties were the reason that PGE₁ as a first PG has been widely used since 1973 for the treatment of cardiovascular diseases, mainly in patients with advanced peripheral vascular disease. Patients were treated intra-arterially in whom vascular surgery or other therapeutic measures were not considered successful and where amputation seemed to be unavoidable. The reported results were described as encouraging and, consequently, PGE₁ was soon administered intravenously. However, no accepted dose regimen was developed and the first controlled study was not published until 1978. The clinical outcomes were discussed controversially. Since 1987, PGE₁ (prostavasin) has been used predominantly intravenously. The compound is registered in Japan, Germany, Italy, Austria, and some other countries for the treatment of ischemic rest pain and trophic ulcerations.

PGs are potent vasoactive agents with a wide variety of other actions that depend on the species and organ tested and the PG used. They are synthesized from 20-carbon polyunsaturated fatty acids containing three, four, or five double bonds. These fatty acids are present in the phospholipids of the cell membranes of all mammalian tissues. PGE₁ is a major PG found in human semen that acts as a vasodilator, a fibrinolytic agent, and an inhibitor of platelet aggregation. In addition,
PGE₁ has been shown to affect protein kinase C, calcium movement, and adenylyl cyclase yielding a multitude of physiological effects. PGE₁ has been reported to benefit patients with significant peripheral vascular disease and limb-threatening ischemia[7]. The routes of infusion may be either intravenous (IV) or intra-arterial. Previously, Strecker et al. reported the use of an implantable port with its catheter placed mainly (9 of 10 patients) toward the periphery of the leg for intra-arterial PGE₁ infusion.[8-10] Disadvantages of the intra-arterial infusion could be the presence of local side effects as rubor, swelling, and pain; on the other hand, the easiest speculated IV route needs a significantly increased PGE₁ dosage (up to four times) to achieve the same to the arterial route effectiveness. Usually, 90% of PGE₁ undergoes metabolic degradation by the first passage from the lung parenchyma. The need of such increased dosage makes the IV treatment problematic especially in patients with borderline cardiac or renal function; by the intra-arterial application of 20 μg of PGE₁ (a quarter of the dose required for IV delivery), systemic adverse effects such as hypotension (due to vasodilatation), lung edema, or cardiac failure are significantly decreased. Increasing doses of PGE₁, given intravenously do not influence the hemodynamic parameters up to a dosage of 1500 ng/min. Intra-arterial administration of a mixture of nucleotides and nucleosides in therapeutic doses induces an increase in the blood flow volume at rest of up to 400%. With dosages of 20 ng/min and more, intra-arterial administration of PGE₁ induces only a slight increase in the blood flow volume of the extremity under treatment. The therapeutic effects of the substance, therefore, are probably more due to other mechanisms of action than to hemodynamic effects.[10]

Peripheral arterial disease has a significant impact on the quality of life. Pain, fear of limb loss, increased inactivity, and poor lifestyle choices such as continued smoking also further debilitate these patients. Surgical and endovascular procedures have affected this outcome for many but carry the added risk of procedural complications and mortality for this group of high-risk individuals. Risk factor management and medical therapy carry little risk and can also improve functional outcome for many of these patients. The cost of therapy is a concern in the chronic ischemia patients and this is also seeming to be in favor of PGE₁ infusion therapy.[11]

In large number of elderly patients aged between 50 and 75 years, the arterial disease is prevalent (1%-7%) and they present with intermittent claudication. Lifestyle modification, control of hypertension, statin therapy with adequate diabetes management there can be improvement in the claudication distance in few patients with different grades of peripheral arterial disease. Also, on the bright side, we are seeing the exciting new developments in endovascular treatments, particularly better balloons, stents, drug-eluting stents and drug-eluting balloons, atherectomy devices, as well as many others that would allow us to better treat lesions that are blocking arteries and causing problems for patients. The problem, of course, is that all these new treatments are expensive and they have to be proven effective, in terms of both outcomes and cost as said by Frank J. Veith in his paper “The Future of Vascular Surgery: The Good and the Bad.” PG infusion therapy has been helpful in patients where such new reconstructive procedures are not feasible or failed and also as an adjunctive when there is residual ischemia after the revascularization procedures.

PGE₁ infusion therapies in association with thrombolytic therapy have been tested and used in some centers to improve the results. This combination was used with a hope of getting the synergistic effect. Recanalization of femoral artery occlusions is difficult and different forms of intra-arterial lysis or mechanical procedures have been described in the past few decades. A study was done to find the benefit of prolonged intra-arterial lysis with recombinant tissue plasminogen activator (rt-PA) in combination with PGE₁, followed by angioplasty. Forty-three patients (age 60.4 ± 14.3 years) with peripheral arterial occlusions older than 3 months and longer than 10 cm were treated with intra-arterial rt-pA (3 mg in 3 h) followed by PGE₁ (2.1 ml/h for 3 h, concentration: 20 μg/50 ml NaCl) in alternating order. Treatment times ranged from 1 to 7 days (2.9 ± 1.6). Doses of 26.5 ± 21.9 mg rt-PA and 20.4 ± 16 μg PGE₁ were used. Whenever possible, angioplasty was performed after passing wire through the lumen. Recanalization was achieved in 47 of 85 arterial segments with re-occlusion in 9 segments. The arterial perfusion was deteriorated only once due to peripheral embolism. Other adverse effects included one case of retroperitoneal and one case of intra-crural bleeding and one pseudoaneurysm. Kröger et al. concluded that chronic arterial occlusions, which do not respond to conventional angioplasty and/or short-term fibrinolysis recanalization, may be achieved in about 50% by means of prolonged alternating application of rt-pA and PGE₁.[12]

**Evolution of Prostaglandin E1 Infusion Therapies at NIMS**

We started using the PGE₁ in the late 1980s to relieve the rest pain, heal ulcers in ischemic legs. It was also used for limb salvage in acute on chronic ischemia patients with viable limbs but not suitable for reconstruction surgery and interventions or who had failed reconstructive procedures. We soon noticed that a single admission and 1 week of injection PGE₁ was not sufficient to get the expected results. Depending on the symptoms, we continued the PGE₁ infusion for 2–3 weeks. However, patients felt it difficult to stay in the hospital for 2 or 3 weeks. We understood that the metabolism of PGE₁ is complex and metabolites of the PGE₁ are biological active for longer periods. The metabolites of metabolites may be more active for different durations. We have given 500 mcg of PGE₁ in week and discharged with partial relief of pains and asked them to come back after 3 or 4 weeks or earlier for the next dose of PGE₁ infusion. The majority of the patients turned up after 4 weeks when the symptoms started again.
Soon, we realized that monthly PGE₁ therapies are working and preferred by the patients. The symptoms such as pain, ulcers got better and walking improved. Toward the end of 6 months after the completion of 6 monthly cycles of PGE₁ infusion, they were free from rest pain, ulcers healed well with improved walking. We observed that most of the patients showed personally satisfied (independent patient interviews) with relief and improvement after completion the 6 cycles of PGE₁ infusion therapy. During the next 10 years' period, our confidence and experience with the use of PGE₁, along with improved evaluation and grading of ischemia of extremities in patients with the help of noninvasive vascular laboratory and use of portal Doppler probe for bedside examination. Then, injection PGE₁ was also made easily available in the pharmacy market without difficulties. The use of the medication, dilution of drug was better understood by technologists, nurses who regularly setup the infusion pump in the vascular surgery wards. During the same period, we also started the vascular technology, vascular nursing courses in our hospital. We developed a protocol for infusing the PGE₁ intravenously (peripheral IV line) for limb salvage in critical limb ischemia in the extremities as shown in Figure 1. Initially, we gave PGE₁ infusion throughout 24 h, but later we stopped during the night time as the patients wanted to be free from the IV lines and tube dangling and disturbing the sleep. Injection PGE₁ is available as 500 mcg vials. We dilute it and give 100 mcg daily (during the day time for 10 h) for 5 days. We continue injection PGE₁ infusion (500 mcg) every month spread over 5 days, that is, 100 mcg daily for 5 days for 6 months. Patients felt that 5 days is a long period and requested it to be shorter. Then, it has been reduced to 3 days hospitalization in all those patients with good relief of pain, healing of ulcers with improvement of ankle pressures by 10–20 mmHg from the 2nd month onward. After that, we have followed this protocol and it remained stable for the last 15 years with very little modifications occasionally. Patients’ compliance is exceptionally good (90%).

In the late 1990s, we have used intra-arterial PGE₁ infusion therapies with and without thrombolytic therapies which corresponded with the introduction of endovascular therapies in our unit. Injection urokinase or streptokinase and injection PGE₁ were given through the side port of the intra-arterial sheath in critically ischemic patients who are found not suitable for reconstructions after angiogram. However, the patients had difficulty in holding the painful leg without movement as there is intra-arterial sheath. Some patients developed problems related to the intra-arterial sheath such as groin hematomas and peri-sheath bleeding. We stopped intra-arterial infusions in combining the thrombolytic agent and PGE₁. We noted that some centers were placing special catheters and ports intra-arterially for long-term intermittent infusion of the PGE₁. The cost of these procedures was more and patients needed special education to keep the catheters safe and free from infection. We never used intra-arterial ports for PGE₁ infusion in our center. Patients receiving intra-arterial and PGE₁ infusions were requiring ICU admissions after placement of the arterial sheath for the close monitoring for bleeding complications. That increased the cost of treatment. Hence, slowly that procedure was went out of practice. We continued the IV infusion of the injection PGE₁ in our hospital. In our annual evaluation, limb salvage was found to be 85% at the end of 6-month follow-up. At the same time, 90% of the patients regularly come back for the monthly injection therapies as they felt good relief. The compliance to the treatment protocol was good as there was minimal expenditure and they could note the monthly improvement in their clinical condition along with all other adjunctive medical therapies to control their systemic illnesses. Smoking cessation was achieved in 3 months after three or four counseling sessions in the ward and outpatient clinic. We generally do not amputate the dry gangrenous toes till their symptoms are well controlled with improvement of objective signs of ischemia. In general, the gangrenous toes are left to fall off spontaneously or facilitated by doing amputation under local anesthesia when the patients are very particular about the same. Attention is also given to the foot wear and the patients are advised avoid minor injury to the ischemia feet. Recently, we also published a paper concluding that there is a significant effect of injection PGE₁ on ankle brachial index
in ischemic patients along with limb salvage at the end of 6 months course of injection PGE\(_1\) infusion therapy.

There are many different regimens with different durations of the injection PGE\(_1\) infusion therapy described in literature. PGE\(_1\) analogs were also tested for their efficacy in the clinical practice. It was proposed that these PGE\(_1\) analogs will deliver active drug to the site of action at adequate doses for sufficient duration. One of them, Lipo-ecraprost, is a lipid-based formulation of a PGE\(_1\) analog. In a double-blind, randomized (560 patients), placebo-controlled study, the effect of Lipo-ecraprost (60 μg) on 6-month amputation rate was studied after giving the medication intravenously for 5 days in a week for 8 weeks by following them for 6 months. Brass et al. said concluded that lipo-ecraprost failed to modify the 6-month amputation rate in patients with critical leg ischemia who were not candidates for revascularization. However, the duration of the medication was given only for 8 weeks. One can hope that if the medication was continued for 6 months, the result could have been different. We strongly advocate medication for 6 months and follow-up at regular intervals for 6 months.[14]

Recently, another large study (ESPECIAL) was reported by Lawall et al. This is a randomized, placebo-controlled, multicenter trial on 840 patients with Fontaine stage IV ischemia. In this study, medication was given for 4 weeks only. Although they have given medication daily, the total duration of 4 weeks will be inadequate for the controlling and reversing the ischemic state of the limb. The authors concluded that the alprostadil superiority over placebo could not be shown from this study.[15]

The mechanism of action and pharmacokinetics of PGE\(_1\) are only partly understood as they seem to be complex [Figure 2]. It is important to note that intravascular half-life of injection PGE\(_1\) is very short, but the metabolites of PGE\(_1\), are biologically active and so the effects are prolonged. Some assume that the benefits of PGE\(_1\), are sustained for longer duration than the presence of known metabolites (measured) in the laboratories. Cawello et al. studied the metabolism and pharmacokinetics of PGE\(_1\) administered by IV infusion in human subjects after giving 60 mcg PGE\(_1\). They measured plasma concentrations of PGE\(_1\), 13, 14-dihydro-PGE\(_1\) (PGE0) and 15-keto-PGE0 using highly specific and sensitive method. It is important to know that PGE0 concentrations were 8 times higher during the PGE\(_1\) infusion than during the placebo infusion. At the same time, 15-keto-PGE0 plasma concentrations were 20 times higher. Some suggests that the metabolites of metabolites continue to be active for longer periods than observed in the laboratories. This may be explaining the benefit we are seeing in the monthly injections of PGE\(_1\), in our clinical practice. We are able to get the optimum clinical benefit to the patients with monthly cycles of PGE\(_1\) for 6 months.[16]

In conclusion, we know that the PGE\(_1\) infusions are safe and working in our patients by relieving the rest pain, healing the ulcers, and improving the limb salvage rates when the known revascularization procedures failed or not feasible. The mechanism of action through biologically active metabolites needs to be understood more in detail. It is also observed that other forms of PGE\(_1\), such as liposome tagged PGE\(_1\), are not giving the similar results. The future of PG infusion therapies depends on the progression of scientific research in understanding the mechanism of action of PGs in the arterial ischemia patients.

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### Conflicts of interest
There are no conflicts of interest.

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