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Intravenous infusion of prostaglandin E1 in ischemic ulcer and rest pain for extremities due to peripheral vascular disease

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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. The original research of benefitted 35 cases in last 5 years is presented here.

Background: As a General surgeon we use only analgesics and anti-platelet agent aspirin for severe ischaemic limbs with rest pain. We could not improve patient's quality of life with these medications. Enough of medicine literature says prostaglandins E1 improves microcirculation, stop tissue damage due to ischemia and relief from rest pain.

Methods: In this study we included both gender patients above age of 34 years who had ischemic changes associated with peripheral vascular disease and rest pain. We infused intravenous prostaglandins E1 and studied them for improvement in soft tissue ischemic changes and in rest pain.

Results: clinical success was evaluated according subjective grading and relief of pain. Patients in these studies had a pain score from 6 onwards as per Wong-Baker FACES pain rating scale improved to 2-4. We also studied them for Fontain and Rutherford staging and scoring system, which improved from III b to II-I and from 4 to 2-1 respectively.

Conclusions: Intravenous infusion of PGE1 alprostadil on 5 days a cycle basis, in selected patients with severe rest pain and ischemia seems to be very effective, without any serious complications.

Keywords: Extremities ischemia, extremities rest pain, PGE1 intravenous 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 ^[1]. PG E1 (PGE1) was first isolated in 1957 by Bergström and Sjövall ^[2]. They discovered the basic chemical structure to be unsaturated fatty acids arachidonic acid with 20 carbon atoms where five are structured as a ring. They are a subclass of eicosanoids and the prostanoid class of fatty acid derivatives. In 1976, prostacyclin was discovered as a potent inhibitor of platelet function and as a strong vasodilator. Both PGE1 and PG12 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 ^[3]. 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 ^[4]. The clinical outcomes were discussed controversially. Since 1987, PGE1 (prostacyclin) has been used predominantly intravenously ^[5].

The fatty acids from which PG derived are present in the phospholipids of the cell membranes of

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all mammalian tissues [6]. 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 adenylate 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, 9, 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.

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 favour of PGE1 infusion therapy [11].

In large number of elderly patients aged between 50 and 75 years, the arterial disease is prevalent (upto 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. 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 procedure.

In our study PGE1 infusion had been given as a treatment of choice with small and medium size vessels involved patients where interventional radiology and surgery is not possible and not helpful.

The purpose of the study is present our results after short-term (9 weeks to 12 weeks) intra-venous infusion therapy of PGE1-alprostadil via peripheral line in patients with severe rest pain and ischemic tissue changes.

Methods

Thirty-five patients (men and women 30:5; age range: 34-71 yrs.) with severe rest pain (Rutherford stage 5 or Fontaine's stage III) and Wong-Baker FACES 6 plus pains score were included into the study.

20 of the males had Buerger's disease. 2 of the female patients had Raynaud's disease with upper extremities involvement. (group A)

The rest had extensive peripheral atherosclerotic changes due to long standing diabetes. (group B)

The following pain scores were used for the study.

| Rutherford stage | Fontain stage | Descriptions |
|------------------|---------------|---|
| 0 | I | Asymptomatic |
| 1 | II a | Mild claudication |
| 2 | II b | Moderate claudication |
| 3 | II b | Severe claudication |
| 4 | III a | Rest pain |
| 5 | III b | Ischaemic ulcers digits of the foot (minor tissue loss) |
| 6 | IV | Severe ischaemic ulcers or gangrene (major tissue loss) |



All patients properly work up with haematological investigations which includes haemoglobin, complete blood count, Bleeding time, clotting time, blood sugar levels, Lipid profile, Liver function test and renal function test. Cardiac profile such as ECG and 2D echo. For arterial status arterial doppler study and CT angiography.

All patients showed a very poor run-off with total occlusion of all three vessels dorsalis pedis, posterior tibial and anterior tibial slightly distally to trifurcation. four patients with Buerger's disease had additional involvement of the popliteal artery. Two female patients had Raynaud's disease with dry gangrene of tips of the fingers of upper extremities. No patient was suitable for by-pass surgery because on selective CT arteriography no

adequate distal vessels were identified. All patients suffered from significant rest pain, and one type of amputation could be speculated for them as the only potential treatment of choice.

All patients were admitted and intravenous PGE1 therapy were given. We used one ampoule of 500 microgram of 1 ml for one cycle for average 50kg. adult patient.

Take one ml solution in syringe and dilute it to 5ml with distilled water. So, each ml contains 100 micrograms of PGE1 to be added in 500ml of normal saline and infused slowly for 8 hours in a day for five days. Same cycle to be repeated after 3 weeks. Three such cycles to be infused to the patient.

Following things to be monitor while giving infusion

1. Vital signs for fever and bradycardia, BP for hypotension and ECG
2. Respiratory rate and respiratory depression or apnoea
3. Hypersensitivity to prostaglandin E1

Results

The peripheral intravenous line had taken and infusion had been given without any significant complications.

All of the patients experienced significant decrease of the pain from the first cycle which continued through the following cycles within subsequent weeks.

All 22(group A) patients experienced moderate to almost complete relief in rest pain and stagnation of further ischemic soft tissue changes. Some of the patients of group B had Buerger's disease with occlusion of the popliteal artery and no

run-off peripherally.

All 13 (group B) patients due to diabetic atherosclerosis experienced significant decrease of pain and improvement in ulcer healing.

No thrombophlebitis or any side effects of drug occurred during the follow-ups. No significant changes noted in the brachial-tibial index or arterial doppler in any patient.

Table 1: Pain Scores of patients before and after PGE1 infusion therapy

| Pain score system | Group A before 22 patients | Group A after 22 patients | Group B before 13 patients | Group B after 13 patients |
|-------------------------|----------------------------|---------------------------|----------------------------|---------------------------|
| Fontain Score | III-IV | II b (22) | III-IV | II b (13) |
| Rutherford-Becker score | 4 | 1-2(12) 3(10) | 4 | 1-2 (13) |
| Wong-Baker Faces Pain | 8-10 | 2-4 (12) 4-6(10) | 8-10 | 2-4 (13) |

Table 1 shows all patients from group A and group B had improvement in all three scores. diabetic pathology Group B pvd had better improvement than Group A, which includes Buerger's and Raynaud's disease. Scoring system of Fontain and Rutherford also shows improvement in ulcer healings. In brackets number of patients are mentioned.

Table 2: Number of patients relieved of pain with cycles

| Number of Cycle | Group A 22 patients | Group B 13 patients |
|-----------------|---------------------|---------------------|
| Cycle one | 12 | 8 |
| Cycle two | 6 | 4 |
| Cycle three | 4 | 1 |

Table 2 shows maximum numbers of patients responded to first cycle of drug therapy and remaining responded to next cycles.

It has been observed that there is tremendous amount of recovery in rest pain after first cycle in 57.14% of patients. 28.57% recovered after second cycle and remaining 14.29% recovered after third cycle,

It has been also observed that there are no further ischemic tissue damage and improvement in wound healings.

Discussion

The mechanism of action and pharmacokinetics of PGE1 are only partly understood as they seem to be complex.

It is important to note that intravascular half-life of injection PGE1 is very short, but the metabolites of PGE1 are biologically active and so the effects are prolonged. Some assume that the benefits of PGE1 are sustained for longer duration than the presence of known metabolites (measured) in the laboratories.

Intravenously infusion of PGE1 in patients with severe peripheral vascular disease has been well documented to be a safe and effective method of treatment in this group of patients who have a very limited-if any-choice of treatment [3, 7, 8]. The easiest speculated intravenous route needs a significantly increased PGE1 dosage (up to four times) in order to achieve the same to the arterial route effectiveness, since up to 90% of PGE1 undergoes metabolic degradation by the first passage from the lung parenchyma. But in our study we did not come across any complications of drugs.

Theoretically a very small portion of the total amount of PGE1 does not reach the extremity. Additionally, we used in our protocol the maximum quantity PGE1 as described in the literature. These two factors contribute additively to reach maximum response and best clinical outcome.

The clinical result obtained in our patients enhances the results of previous studies for good clinical short success. Clinically important relief from rest pain was achieved in all of the patients. The ten patients who had moderate response were

patients with Buerger's disease. Smoking may reduce the effectiveness of that type of treatment in this specific subgroup of patients.

According to the literature many different examinations exist that can objectively document changes of perfusion in the area of interest. Evaluation with transcutaneous PO₂, laser Doppler flow, and volume flow may show improvements of microcirculation and limb perfusion and have been adequately described [11]. In our study we tried only arterial doppler study which obviously unable to show any improvement in blood flow.

Conclusion

In conclusion, intra-venous infusion of PGE1 via a peripheral line in patients with rest pain has good short-term clinical success by creating significant peripheral vasodilatation. We think this is an interesting new figure in this type of treatment. Further studies with more patients may be needed to document these observations.

We are also know that the PGE1 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. 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.

Conflicts of interest

There are no conflicts of interest.

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