TREATMENT OF CRITICAL LIMB ISCHAEMIA WITH PROSTAGLANDINS

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Abstract

Critical limb ischaemia is defined as ischaemic rest pain for 2 weeks or necrosis/gangrene of a toe, foot or ankle, corresponding to stages III-IV according to Fontaine classification of peripheral vascular disease. The aim of this paper is to evaluate the efficacy of PGE1 administred as an intravenous infusion in diabetic patients with critical limb ischaemia. There were selected to receive PGE1 16 diabetic patients (7 men and 9 women) with critical limb ischaemia. Stage III peripheral arterial disease was identified in 10 patients (62.5%) and stage IV in 6 patients (37.5%). None of the patients was a proper candidate for reconstructive surgery (arterial stenting or bypass). PGE1 was administred by slow intravenous infusion of 2 ampoules (40 micrograms PGE1) in 250 ml isotonic saline solution twice daily for 20 consecutive days combined with conservative treatment. After 3 weeks of treatment all 10 patients with peripheral vascular disease stage III reported pain relief or even disappearance of rest pain. Ulcers healed completely in 3 (50%) patients with stage IV peripheral vascular disease, while the other 3 (50%) patients underwent below-knee (trans-tibial) amputations. PGE1 treatment was effective in diabetic patients with major amputations avoided in all 6 patients with stage IV peripheral vascular disease. Intravenous treatment with prostaglandin E1 resulted in amputation level decrease, ulcer healing, improvements in rest-pain, pain-free walking distance and quality of life.

key words*: critical limb ischaemia, diabetes mellitus, prostaglandin.*

Background. Critical limb ischaemia (CLI), defined for the first time in 1982 by P. R. F. Bell, is a manifestation of periferal artery disease which describes patients with typical chronic ischaemic rest pain or patients with ischaemic skin lesions, either ulcers or gangrene. The term should only be used in relation to patients with chronic ischaemic disease, defined as the presence of symptoms for more than two weeks [1]. These criteria correspond to stages III-IV of Fontaine classification of peripheral vascular disease (see Table 1). Observational studies show that one year after diagnosis 25% of patients experienced a major amputation, 25% had died and only 50% survived without requiring a major amputation, even though some of them still have pain at rest, ulcers or gangrene. Data refer to patients in whom surgical revascularization procedures were not possible

[1]. Management of peripheral vascular disease include modification of cardiovascular risk factors (cigarette smoking, diabetes mellitus, older than 40 years, hypertension, hyperlipidemia, and hyperhomocystinemia), "walking therapy", pharmacotherapy and surgical therapy (see Table 2) [2]. The primary goals of critical limb ischaemia treatment are to relieve ischaemic pain, heal ulcers, prevent limb loss, improve patient function and quality of life and prolong survival [1]. Prostaglandins E_1 (PGE_1) are the only pharmacological treatment recommended by TASC II (Inter-Society Consensus for the Management of Peripheral Arterial Disease) in peripheral vascular disease Fontaine stage III and IV (critical limb ischaemia).

Prostaglandins, derivates of "prostanoic acid", are important biologically molecules present in almost all cell and tissues, a collection of short-live chemical mediators which control smooth muscle contraction, exocrine gland secretion, and components of the immune response [3]. They received their name because they were first detected in human seminal fluid obtained from the prostate gland. They are named as PG from prostaglandin, followed by another letter from A to H depending upon the side group of the cyclopentane ring and by a subscript indicating the number of double binds in the structure. The first positive results after PGE_1 administration in patients with obstructive artery disease were published in 1976, in Europe, by A.G.Olsson and L.A.Carlson [4]. Since then several clinical trials have reported a marked and persistent improvement of symptoms in patients with end-stage peripheral vascular disease: disappearance of pain at rest - 50%, pain relief - 37-40%, partial healing of trophic ulcers - 40-50 %, complete healing of trophic ulcers - 10-20%, an increase of 75% of the pain –free walking distance [5].

Vasaprostan (PGE_1, alprostadil) is a drug approved to treat peripheral vascular disease stage III and IV of Fontaine classification, particularly when other therapies (physiotherapy, thrombolysis, reconstructive interventions) are not viable alternatives or were unsuccessful [5]. Therapeutic effects of Vasaprostan are based mainly on the vasodilator effect in the arterioles and precapilare sphincters [6], but recent studies have revealed the importance of aditional effects for efficacy in the treatment of critical limb ischemia:

- stimulates local blood circulation and angiogenesis,
- increases red cell deformability and platelet life,
- protects endothelial cells,
- prevents vascular storage of lipids,
- prevents the release of growth factors,
- improves fibrinolysis,
- improves microcirculation [7].

Vasaprostan is a dry powder packed in glass ampoules containing 20 μg alprostadil (PGE_1) for infusion for parentheral (intravenous or intra-arterial) administration. The recommended dose is 40 μg alprostadil (2 ampoules) diluted in 50-250ml of isotonic saline solution, administered twice daily by intravenous infusion over a time of 2 hours or 10 μg alprostadil (1/2 ampoule) diluted in 50 ml of isotonic saline solution administred once a day by intra-arterial infusion over a time of 60-120 minutes. When necrosis is present, the intra-arterial dose can be raised to 20μg as long as the patient's tolerance is satisfactory. The benefit of vasaprostan treatment must be assessed after 3 weeks: if the patient did not respond the treatment should be stopped. Treatment duration should not exceed 4 weeks

[5]. The aim of this paper is to evaluate the efficacy of PGE1 administred as an intravenous infusion in diabetic patients with critical limb ischemia when the procedures of reconstructive surgery are not possible.

Material and methods. There were selected for treatment 16 diabetic patients with critical limb ischemia: 10 patients (62.5%) with stage III and 6 patients (37.5%) with stage IV diabetic arterial disease Fontaine classification. The diagnosis of peripheral artery disease and obstruction headquarters were established by physical examination with special attention to the pulses, auscultation of arterial bruits and inspection of color changes, Doppler ultrasonography and magnetic resonance angiography. Laboratory investigations showed high obstructions which would not allow reconstructive surgical treatment and would have required major amputations. Vasaprostan was administred by slow intravenous infusion of 2 ampoules (40 micrograms PGE_1) in 250ml isotonic saline solution twice daily for 20 consecutive days combined with conservative treatment. Surgical wound toilet, necrectomy and limited toe amputation were performed in 4 patients during the treatment.

Results and discussion. Lot studied had an average age of 67±7.5 years and an average age of diabetes of 18.2±3.2 years. Of the 16 participants, 9 (56.25%) were women and 7 (43.75%) men. By bringing together the medical history, clinical and laboratory investigations, the diagnosis of peripheral vascular disease stage III (rest pain) was established in 10 patients and peripheral vascular disease stage IV (ulceration or gangrene) in 6 patients. The indication for surgical reconstruction or intervention endovascular intervention was not applicable to any patient. After 3 weeks of treatment all 10 patients with peripheral vascular disease stage III reported pain relief or even disappearance of rest pain. In 50% of patients with stage IV peripheral vascular disease, ulcers were healed completely, while the other 3 (50%) required amputations in the upper third of the calf, which is still a benefit given that all participants prior to Vasaprostan treatment have had indication for major amputations. On overall group, 10 patients (62.5%) reported relief or disappearance of rest pain, 3 patients (18.75%) experienced complete healing of ulcers and other 3 patients (18.75%) required calf amputations. Adverse effects observed during intravenous administration were similar to those described in the literature: redness, pain and swelling in the infused member, headache, chills, sweating, flushing, gastrointestinal disorders (nausea). All adverse effects were mild and resolved after stopping the infusion.

Conclusions. Vasaprostan treatment was effective in diabetic patients with major amputations avoided in all 6 patients with stage IV peripheral vascular disease. Despite the small number of participants, therapeutic effects cited in the literature were reproduced in our lot:

- reducing the number/level of amputations,
- partial/total ulcer healing,
- disappearance or relief of rest-pain,
- increasing pain - free walking distance,
- improving the quality of life.

As international guidelines recommend, conservative treatment with PGE1 should be considered in patients with critical limb ischemia for symptomatic and functional improvement as for healing trophic lesions, particularly in cases where amputation is imminent.

Table 1

Fontaine classification of peripheral vascular disease
Stage I: no symptoms Stage II: intermittent claudication Stage III: resting pain Stage IV: trophic lesions (ulcer or gangrene)

Table 2

Management of peripheral vascular disease[3]
1. Management of cardiovascular risk factors: • Diabetes treatment ($HbA_1c<7\%$) • Hypertension treatment (JNC VII) • LDLc<100mg/dL • Smoking cessation • Antiplatelet treatment 2. Walking therapy 3. Pharmacotherapy 4. PGE_1 if symptoms worsen with the above treatment 5. Endovascular or surgical therapy

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