Medical Management of Peripheral Artery Disease in Patient with Diabetic Foot Ulcer: A Case Report

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Abstract
Critical limb ischemia (CLI) is common in patients with peripheral artery disease (PAD) and concomitant diabetes. Minor leg or foot trauma may lead to ulceration in patients with PAD and diabetes. These patients are at risk due to microcirculation damage and associated diabetic sensory neuropathy and neuroischemia. The reduced ability to combat infection resulting from poor perfusion in patients with diabetes worsens the ulceration. A 63-year-old man presented with right foot dina and an ulcer that had been present for 6 years. Initially the patient developed an ulcer on the plantar aspect of his right foot. The ulcer worsened and required amputation of his 1st, 2nd, 3rd and 5th toes about four years ago. Since then the ulcer was slow to heal despite debridement, courses of antibiotics and visits to diabetic foot clinic. He later presented with severe pain and was admitted for management with prostaglandin E1 (Alprostadiil). There was complete healing of the ulcer by the 15th day. The patient developed an ulcer on the plantar aspect of the right foot. About four years ago, the ulcer worsened, ultrasound and ankle brachial index results were abnormal. The stage of the ulcer gave no indication or option for vascular bypass and angioplasty thus necessitating amputation of his 1st, 2nd, 3rd and 5th toes. Since then the ulcer was slow to heal despite debridement, courses of antibiotics and visits to diabetic foot clinic. He has also been experiencing severe pain over the years.

Keywords: Peripheral Artery Disease; Medical Management; Diabetes; Foot Ulcer

Abbreviations
PAD: Peripheral Artery Disease; CLI: Critical Limb Ischemia; ABI: Ankle - Brachial Index; DFS: Diabetic Foot Sepsis; CBG: Capillary Blood Glucose; PO: Per Oral; IV: Intravenous; PG: Prostaglandin; NaCl: Sodium Chloride; q3h: every 3 hours for 5 days.

Introduction
Diabetic patients who are 50 years of age and above usually have 29% occurrence of PAD [1]. The Rotterdam study reported a higher percentage of 16% for females’ and 11.9% for males in diabetic patients with abnormal ankle - brachial index (ABI). These were compared with diabetic patients without peripheral artery disease and abnormal ABI. The PAD percentage was lower for female with 6.3% and 6.7% for male [2]. In diabetic patients older than 65 years of age there was approximately four times occurrence of PAD in the study of cardiovascular health [3]. Type 2 diabetes mellitus is considered a polygenic disease that requires acquired factors and genetic parameter to manifest itself [4]. The acquired factors may be modifiable, which include obesity, sedentary activity or non-modifiable such as aging [5]. Diabetes has been reported to be a major independent predictor of death in patients with intermittent claudication [6]. Critical limb ischemia (CLI) is more likely to occur in diabetic patients with PAD than in patients with PAD not associated with diabetes [7]. Ulceration and infection of leg or foot trauma in diabetic patient is often due to the microvascular pathophysiology of the lower extremity which includes neuroischemia and sensory neuropathy [6,7]. The peripheral sensory neuropathy causes the diabetic foot not to respond to dynia and temperature sensitivity. The patient is therefore not capable of identifying strain and compression on the affected foot. Foot damage can go unnoticed because sensation is limited [7]. All these pathological factors contribute to increasing the incidence of CLI. In addition, these factors can worsen the ulceration due to the microcirculation damage and reduce the ability to combat infection secondary to poor perfusion [6,7]. Amputation may be required to prevent sepsis and death. Vascular bypass and angioplasty outcomes for PAD are unfortunately less satisfactory in patients with diabetes.

Case Report
A 63-year-old man presented with right foot pain and ulcer for 6 years on the plantar aspect of his right foot. About four years ago, the ulcer worsened, ultrasound and ankle brachial index results were abnormal. The stage of the ulcer gave no indication or option for vascular bypass and angioplasty thus necessitating amputation of his 1st, 2nd, 3rd and 5th toes. Since then the ulcer was slow to heal despite debridement, courses of antibiotics and visits to diabetic foot clinic. He has also been experiencing severe pain over the years. He presented with severe pain and was admitted for management with prostaglandin E1 (Alprostadiil).

On review of systems, nothing was significant. Past medical history revealed cardiovascular risk factors including current smoking (1/2 pack per day for 10 years) and a 15-year history of diabetes and hypertension. His first hospital admission was about four years prior for right diabetic foot sepsis (DFS). The 2nd hospital admission was a month later for right DFS plus amputation of right 1st, 3rd, 4th and 5th toes. Medications included metformin, glipizide, enalapril and aspirin. On physical examination, he was hypertensive with a blood pressure of 180/100 mmHg, blood glucose (CBG) level was 5.9 mmol/L (126 mg/dl). On lower extremities, there was amputation of right 1st toe, 3rd, 4th and 5th toe on the right foot. There was ulcer with dark and necrotic area of 3 cm x 4 cm at the plantar surface middle region, cold to touch with smooth skin and loss of hair at pretibial area of right leg. The left foot showed no significant findings. The patient was admitted and laboratory investigation was unremarkable. The patient was prescribed enalapril, glipizide, metformin, antibiotics –cloxacilin, gentamicin and metronidazole.
In addition, prostaglandinE1 (alprostadiil) treatment was as follows: 1st cycle with dose of 60 mcg in 250 ml of isotonic NaCl solution q3h.
solution, q 3h x 5 days. Side effects such as headaches, dizziness, hypotension, and bradycardia were monitored. On review of the patient, vital signs were stable and there were no significant side effects of prostaglandin E1. The patient was therefore discharged on the 5th day. Six weeks later, reassessment was done and there was wound healing improvement with no clinical presentations as before. Second admission was after 6 weeks for second cycle of prostaglandin E1 (alprostadil) with dose of 60 mcg in 250 ml of isotonic NaCl solution, q 3h x 5 days. Side effects such as headaches, dizziness, hypotension, and bradycardia were monitored. On review of the patient on the 5th day, vital signs were stable and there were no significant side effects of prostaglandin and patient was discharged. Reassessment six weeks after the 2nd cycle showed that the ulcer healed completely with no pain (Figure 1).

In spite of the above positive result, 3rd cycle of prostaglandin E1 with dose of 60 mcg in 250 ml of isotonic NaCl solution, q 3h x 5 days was also given to strengthen the outcome. Side effects such as headaches, dizziness, hypotension, and bradycardia were monitored. On review of the patient on the 5th day after 3rd cycle of prostaglandin E1, vital signs were stable and there were no significant side effects of prostaglandin and the patient was discharged.

Discussion

The use of prostaglandins for the treatment of PAD and critical limb ischemia (CLI) is not a recent idea. The healing of ischemic necrosis and ulceration in this patient treated with 60 mcg of prostaglandin E1 (alprostadil) for 15 days is consistent with the report of UCB Biosciences [15] who confirmed superior effect of 40 mcg of alprostadil for patients treated for 12 weeks compared to placebo on the rate of complete healing of ischemic necrosis and ulcerations. Prostaglandin E1 mechanisms of action include peripheral vasodilatation, enhancement of microcirculation, and inhibition of platelet aggregation [12,13]. Intravenous infusion of PGE in patients with severe PAD has been well documented to be a harmless and effective method of treatment in this group of patients who have a very limited choice of treatment [14]. Prostacyclin (PGI2) was found to be active vasodilator and also as an effective inhibitor of platelet activities [14]. PGE1 and PG12 are compounds that are produced endogenously. They attach and use the same receptor surface of their target cells to carry out their chemical activities.

However, the influence of prostaglandins is up till today and a debatable topic in their use for PAD treatment [17–20]. It has been established clinically that the use of prostaglandin reduces claudication, adds to life quality and enhances ability to walk [19].

It can be assumed that after local infusion of prostaglandins there is an enhancement of wound healing, decrease of dynia and a reduction of amputation in approximately 50% of subjects with CLI that have no choice of vascular bypass or angioplasty [20]. Many of the long-term studies in patients with CLI confirmed a reduction in their size of ulcer, need for amputation and dynia [21–24]. On the other hand, there were no significant outcomes in short-term studies in subjects with CLI. Specifically, in many of these studies there was no dynia reduction or healing of ulcer [25–28].

However, in patients with the worst stages of PAD who do not qualify for vascular bypass and angioplasty procedures and treated with PG E1 showed that there was increase in the rate of patients surviving with both legs after 6-months follow up in a meta-analysis. In addition, there was a valuable outcome over placebo on dynia relief and healing of their ulcers [29].

Conclusion

There was healing of ischemic necrosis and ulceration in this diabetic patient treated with 60 mcg of prostaglandin E1 (alprostadil) for 15 days. The pharmacological property as a vasodilator was the reason for prostaglandin to be widely used since 1973 for the treatment of cardiovascular diseases [30], mainly in patients with advanced PAD [31].

More studies should be done on clinical efficacy of prostaglandin E1 in order to come up with a standard regimen protocol. Whenever such work has to be done, it should include therapeutic dosage comparisons and use of prostaglandin products from only one manufacturer as products from different manufacturers will not be of the same quality. Secondly, health sector should do more on monitoring, encouraging, educating and enforcing preventive strategies on modifiable risk factors of diabetes thereby preventing and reducing its disastrous renal and cardiovascular complications.

Conflict of Interest

The author certifies that there is no conflict of interest with any financial/research/academic organization, with regards to the content/research work discussed in the manuscript.

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