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Case Report

Epoprostenol & Its Use in Microvascular Surgery – A Useful Aid to Flap Salvage Secondary to Recalcitrant Vasospasm?

Suzanne M Beecher[1*], Gráinne Bourke[2,3] and E Jason Kelly[1]

[1]*Department of Plastic and Reconstructive Surgery, Cork University Hospital, Cork, Ireland*
[2]*Department of Plastic Surgery, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom*
[3]*Faculty of Medicine and Health Sciences, University of Leeds, Leeds, United Kingdom*

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ABSTRACT

Systemic intravenous epoprostenol, as well as being a vasodilator, is the most potent inhibitor of platelet aggregation known. Early research carried out on its use in microvascular surgery showed promising results in preventing thrombosis and improving flap survival rates, however interest in its use in microsurgery has diminished in recent years. In this report we describe its use in successful free flap salvage and discuss its role in microsurgery.

Introduction

Epoprostenol is a naturally occurring compound that is produced by the intima of blood vessels. It is also known as prostacyclin and PGI_2. It is a powerful platelet anti-aggregation agent and vasodilator. Research carried out on its use in microvascular surgery showed promising results in preventing thrombosis and improving flap survival rates. There was a wealth of laboratory investigations in the 1980's and 1990's into the use of epoprostenol in microvascular surgery, however interest in the compound has tapered off over the last twenty years. We present a case where epoprostenol was used in flap salvage and discuss its merit in microvascular surgery.

Case Report

We report the case of a healthy 19-year-old male, who sustained a degloving injury to the volar aspect of his left thumb. There was a 6x4cm defect, with exposed bone and flexor pollicis longus tendon. We reconstructed the defect using a free dorsalis pedis flap from his left foot. The flap was anastomosed end-to-end on to the radial artery and its vena comitans, which were out of the zone of injury. At the time of anastomosis, despite patent vessels, minimal flow was noted through the anastomoses and the flap remained pale. Only after topical application of papaverine did the flap revascularize. On postoperative day 2, the flap changed colour and became a deep red with little demonstrable capillary refill. The patient was returned to theatre. Intraoperatively it was noted that there was no blood flow in the artery. The anastomosis was excised and inspected. There was no intimal abnormality or thrombus discovered. The artery was re-anastomosed. Again, there was a lack of adequate flow until topical application of papaverine. As vasospasm was the likely cause of lack of arterial flow, an infusion of epoprostenol at 5ng/kg/min was commenced. It was continued for 4 days postoperatively and then tapered off over 2 days. The flap survived without any adverse events. Whilst the patient was on the infusion, he did have facial flushing and reported a feeling of warmth. His heart rate and blood pressure remained unaffected during the duration of the infusion.

Discussion

Epoprostenol is the most potent inhibitor of platelet aggregation known [1]. It was first discovered by Moncada *et al.* in 1978 [2]. It is a naturally occurring compound that is synthesized by vascular endothelium. It is a

[*]*Correspondence to: Dr. Suzanne M Beecher, M.B., B.Ch., B.A.O., M.R.C.S., M.Ch., M.Sc., Department of Plastic and Reconstructive Surgery, Cork University Hospital, Cork, Ireland; Tel: +353214922000; E-mail: suzub@hotmail.com*

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potent vasodilator, platelet anti-aggregation agent and thrombolytic. It prevents platelets from adhering to normal vascular endothelium. Epoprostenol is used in the treatment of various conditions such as pulmonary hypertension. It is also used in dialysis as an anticoagulant [3]. Epoprostenol has a short half-life of 3 minutes. It therefore requires administration via continuous infusion. The mechanism of action of prostacyclin was investigated by Saniabadi *et al.* They found that prostacyclin disaggregated platelet thrombi that were induced by adenosine 5'-diphosphate and by thrombin but found it to be minimally effective in preventing aggregation induced by collagen and by arachidonic acid [4].

In 1981, Emerson *et al.* were the first to investigate the application of prostacyclin in microvascular surgery [5]. They investigated its use as a topical solution on venous anastomoses intraoperatively in animal models. They found that its use resulted in a statistically significant reduction in microvascular thrombosis. Crabb *et al.* showed similar findings and found that topical prostacyclin at a concentration of 200ng/ml had a similar vasodilatory effect to 2% lidocaine, and its effect was longer lasting when compared to lidocaine [6]. Salemark *et al.* however refuted its use as a topical agent, as in their studies in rabbits, it did not appear to be efficacious [7]. They postulated that epoprostenol leads to reduced vascular muscle tone causing turbulence and vessel thrombosis. This however is the only study describing a negative outcome with epoprostenol. Emerson *et al*. also described the benefit of prostacyclin in improving the survival of random pattern flaps in animal models [8]. In addition to random pattern flaps, epoprostenol has also been shown to improve free flap survival in animal models [9]. Prostacyclin analogues, such as iloprost, have also been shown to improve the survival of threatened free flaps in animal models [10]. However, they may be associated with increased risk of bleeding complications.

Lepore *et al.* compared the use of epoprostenol infusion to other compounds use to improve flow and flap survival [11]. They found the epoprostenol was superior to commonly used drugs such as heparin at improving flow through the flap and improving overall flap survival. Gateley *et al.* first described the use of epoprostenol in humans for cases of free flap salvage in 1996. They reported 2 cases of repeated arterial thrombosis at the time of the primary anastomosis, whereby the anastomosis was revised 4-5 times, and on the final time, they initiated an epoprostenol infusion and the vessel remained patent [12]. They continued the infusion for 24 hours postoperatively. Bonde *et al.* also incorporated the epoprostenol into their protocol for flap salvage [13]. They report 2 cases of flap salvage owing to, in this case, venous thrombosis during the postoperative period. In their cases they report flushing the flap with recombinant tissue plasminogen activator (rtPA) and simultaneously commencing an epoprostenol infusion for 24 hours. Both cases were successful in flap salvage. These are the only clinical cases in the literature describing its benefit in free flap salvage. There can be a concern about systemic infusion of epoprostenol and its effect on the cardiovascular system, owing to its potent vasodilatory effect. The main symptom that can be associated with epoprostenol infusion include facial and palmar flushing, with an associated warm feeling [14]. This was seen in our case.

Epoprostenol can also cause a dose-dependent increase in pulse pressure, which is largely due to a reduction in diastolic pressure [14]. Moncada *et al*. found that, in healthy volunteers, an increase in heart rate and decrease in diastolic blood pressure was noted when epoprostenol was infused at a systemic dose of 20ng/kg/min [15]. However, platelet aggregation can be prevented in doses as low as 2-5ng/kg/min and therefore this is significantly below the dose required to cause a significant systemic effect on blood pressure [14]. In our study, we did not note an adverse effect on blood pressure at a dose of 5ng/kg/min. Interestingly Szczeklik *et al.* found that in healthy volunteers, venous oxygenation improved significantly during prostacyclin infusion, with almost arterialization of the venous blood [14]. This is an interesting concept, as it may bring more oxygenation to flaps and may in theory reduce the incidence of partial flap loss and fat necrosis.

It is difficult to ascertain the beneficial duration of therapy with epoprostenol. Knight *et al.* reported that a survival advantage was seen after infusion of prostacyclin for 30 minutes in animals [9]. Other animal studies showed benefit with continuous infusion for a few days [16]. Further studies are required to determine the optimal duration of treatment. Whilst the optimal duration of therapy is unknown, it is important to note how the infusion should be ceased. A rebound state of hypercoagulability occurs in the first 24-48 hours after cessation of epoprostenol infusion, as first described by Yardumian *et al.* [17]. Therefore, the infusion should be tapered off at the end of treatment to avoid rebound thrombogenesis.

In conclusion, we feel that epoprostenol is an important endogenous compound. The authors use it as first line chemical adjunct for vasospasm in free flap salvage in small children as the risk is greater in this age group. There is a wealth of literature describing its potential benefits in microvascular surgery. Further studies should be undertaken to look at its clinical use in free flap salvage and ascertain the optimal length of treatment.

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