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ORIGINAL STUDY

Tibial corticotomy and periosteal elevation induce angiogenesis in chronic critical limb ischaemia

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Corticotomy and periosteal elevation as a surgical procedure for management of chronic critical limb ischaemia is a relatively new technique. The current study aimed at assessing its safety, efficiency and cost/benefit ratio.

The procedure was performed in 36 patients. Preoperative documentation for age, sex, co-morbidities, ankle systolic pressure, and magnetic resonance contrast angiography was obtained. Early results included evaluation of skin perfusion. Late results involved assessment of wound healing, which was documented with photographs and was graded (healed, healing, resistant, recurrent), pain (intermittent claudication and pain at rest), Kelkar score, procedure morbidity, patient satisfaction and quality of life.

Mean age was 68.03 ± 5.5 years ; 23 patients were males (63.9%) and 13 females (36.1%). Twenty (55.6%) patients had ankle systolic pressure < 50 mmHg and 29 (80.5%) had infra-inguinal vascular disease. Skin perfusion improved in 33/36 patients (91.7%). At final follow-up, 34 patients (94.1%) achieved complete wound healing. Relief from ischaemic rest pain and intermittent claudication was achieved in 86.1% and 55.6% respectively, with 20 (55.6%) patients having an excellent Kelkar score. Only one patient required a major amputation. Morbidity was noted in 17.7% of cases. Patient satisfaction scores at 12 months and at final follow-up were 7.1 ± 1.3, and 8.7 ± 1.7 respectively, on a scale from 0 to 10. Quality of life was markedly improved as compared to the preoperative status (overall score : p = 0.05, mental health scale : p < 0.05 and pain/anxiety domain : p < 0.001).

The procedure appears to represent an interesting tool, which should be evaluated in randomised studies. Our findings support the postulated angiogenic effect of the fracture haematoma.

Keywords : peripheral vascular insufficiency ; corticotomy ; amputation ; revascularisation.

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INTRODUCTION

Chronic critical lower limb ischaemia (CCLLI) is a relentless problem that affects functional status and quality of life (QoL) (*19*). Despite major advances, the condition carries dismal prognosis, with mortality rates ranging from 19% to 54% one year after diagnosis of the condition, irrespective of treatment efforts (*4*). Also, one third of survivors require major amputation within 12 months and 20% of those with intact limbs suffer continuous disease (*18*).

Not only does the disease feature a narrow therapeutic window but it also has a high impact on health economics (*18*). Distraction histogenesis using the Ilizarov technique was recently used to improve the vascular response in CCLLI (*12*). It is a vascular dependent process based on the stress tension principle, deriving pluripotent cell differentiation, coupling angiogenesis with osteogenesis (*17*) and improving the vascularisation of the ischaemic extremity (*9*). However, the patients may suffer from temporary deterioration, non-compliance with the fixator and prolonged time in fixator. The process also has its morbidity related to pin track infection and to the bulky framework (*12*).

Kelkar (*16*) devised a procedure combining trapdoor corticotomy and periosteal elevation, with the aim to stimulate controlled surgical inflammation, with consequent inflammatory angiogenesis. This controlled inflammation is a biologic process that is dependable and predictable, generating neovascularity, and acts as an endogenous bypass conduit improving the circulatory status (*1*).

To the best of our knowledge no clinical report had evaluated this technique since Kelkar (*16*) described it. In this pilot study, the Kelkar technique (*16*) was evaluated in CCLLI patients, with secondary major amputation (below or above the knee) as a primary outcome measure. Both patient centered outcome (pain, wound healing, satisfaction, quality of life) and procedure related morbidity (fracture, wound complications) were evaluated as secondary outcome measures. Magnetic Resonance Angiography ("MRA") with contrast enhancement was used to evaluate the efficiency of the procedure in terms of angiogenesis.

The finite end points were death or major amputation.

PATIENTS AND METHODS

Between March 2004 and January 2006, 36 patients with CCLLI were included in this study. The protocol was approved by the local institutional review board. All patients signed a written informed consent.

Indications for inclusion in this study were patients with CCLLI in case of failure of medical treatment (smoking abstinence – Pentoxifilline – opiates analgesia) with neither surgical nor radiological options of revascularisation, failure of surgical treatment (sympathectomy, revascularisation) or failure of both. Exclusion criteria were patients with impaired inflammatory response, steroid and immune-compromised patients with life threatening complications of limb ischaemia, and patients candidates for primary amputation according to the Trans- Atlantic inter-Society Consensus document on management of peripheral arterial disease (TASC) guidelines (*18*).

The study group included 36 patients with a mean age of 68.03 years (range : 55 to 78) ; 23 (63.9%) were males and 13 (36.1%) females. Twenty (55.6%) patients were diabetics, 27 (75%) had hypertension and 21 were smokers. Previous surgical interventions were lumbar sympathectomy for 7 (19.6%) and revascularisation for 2 (5.8%) patients. The average follow-up was 3.5 years (range : 2 to 4 years).

Preoperatively, patients' demographic data, comorbidities, previous operative intervention and limb evaluation (vascular, neurological, and ulcer type "ischaemic and neuro/ischaemic"), routine laboratory investigations and ankle systolic pressure measured with a Pocket Doppler were documented. Preoperative contrast MRI angiography was performed.

Operative technique

The operation was carried without a tourniquet. With the patient under spinal anaesthesia, a 5-cm long laterally curved incision was made over the lateral aspect of the tibia, 10 cm distal to the knee joint (fig 1a). The corticotomy site was selected on the lateral surface of the tibia near the neurovascular bundles and major muscle bulk. A Kirschner wire was passed along the anterolateral surface of the tibia to guide the direction of the drill bit. Multiple drill holes were made from anteromedially towards the posterior cortex along the endosteal surface,. At the proximal and distal margin of the drilled cortex,

similar drill holes were made from the anteromedial aspect of the tibia towards the lateral cortex. A narrow osteotome connected the drill holes, first anteriorly then anterolaterally to complete the trap-door type cortical window, leaving the posterior perforated cortex intact (fig 1b). This created a trap-door rectangle about 5cm in length with its width corresponding to the anterolateral aspect of the tibia. Using two osteotomes inserted into the anteromedial cortical cut, the posterior perforated cortex was broken manually like a hinge, preserving its periosteum (fig 1c). Periosteal closure was done over the anteromedial corticotomy to keep the broken fragment in place. Multiple small skin incisions were then made along the anterior border of the tibia ; through these incisions the periosteum was elevated, from the tibial tubercle to the medial malleolus, over the medial subcutaneous surface and over the lateral surface of the tibia except at the corticotomy site (fig 1d). The skin and subcutaneous layers were sutured (fig 1e). After completion of the procedure, all existing ulcers were debrided and any obviously gangrenous tissue was excised ; viable tissue was kept.

Postoperatively, intravenous antibiotic was administered for 7 days, the only analgesic used was paracetamol ; the limb was neither elevated nor lowered. Plain radiographs were obtained to assess the corticotomy site (fig 2a), early mobilisation of nearby joints and early ambulation were encouraged (toe-touch weight bearing was allowed during the first two weeks, increased gradually to full weigh bearing when radiographic evidence of fracture healing was obtained). Neither platelets antiaggregants nor anticoagulants were used. Wounds were rechecked after 4 days and patients were discharged after 7 days.

Follow-up

Clinical outcome was assessed every two weeks in the first two months, then every month in the first year, every six months in the second year, then yearly. At each visit the ankle systolic pressure was measured, wound healing was documented with photographs, and radiographs of the leg were obtained. By the end of the fourth month MRA with contrast was performed (fig 2b, c).

The following items were evaluated : the main outcome measure in the form of secondary major amputation (below or above knee), and the secondary outcome measures including patient related outcome (pain, wound healing, patient satisfaction, Quality of life and the global score) and procedure related morbidity (fracture, wounds infection, ulcer and haematoma).

Regarding pain, ischaemic rest pain and intermittent claudication were graded as absent (stage I), not disabling (stage IIA) and disabling in domestic or occupational activity (stage IIB). Wound healing was assessed as "healed" when complete epithelium coverage was achieved, "healing" when the wound was covered with viable granulation tissue, "resistant" when the wound size had increased, with infection, and "recurred" in cases with ulcer recurrence. Global score according to Kelkar (*16*) was used for final evaluation. It was graded as excellent if there was neither ischaemic rest pain nor claudication and wound healing was achieved, good if there were both relief from rest pain and non disabling claudication and wound healing was achieved, fair if there was relief from rest pain but there were disabling claudication and recurrent, non-healed ulcers or delayed healing, and as poor if there was a major amputation. For patient satisfaction, a visual analogue score was used [0 = not satisfied to 10 = maximum satisfaction] and for Quality of life, the 36 item short form health survey (SF-36) was applied (*26,27*).

RESULTS

Preoperatively, the ankle systolic pressure (ASP) was < 50 mmHg in twenty (55.6%) patients and above 50 mmHg in 13 (36.1%) patients. In three (8.3%) patients the cuff could not be applied (all patients had atrophic skin changes, ischaemic ulcers, gangrenous skin patches). Preoperative MRA study revealed 7 (19.4%) patients with aortoiliac disease, 10 (27.8%) patients with superficial femoral artery disease, 3 (8.3%) patients with popliteal disease and 16 (44.4%) patients with tibioperoneal disease.

Early results revealed 33 (91.7%) patients with improved skin perfusion (venous refill, skin warmth-skin brightness).

Over time, 31 (86.1%) patients were relieved from ischaemic rest pain after the 4th month (table Ia). Similarly claudication pain and wound healing status progressively improved over time (table Ib-c). The data were photo documented for dry gangrene of toes and skin patch, heel ulcer (fig 3), and any encountered complications.

At final follow-up, according to Kelkar's scoring system 20 patients (55.6%) had an excellent score, 10 patients (27.8%) had a good score, 5 patients

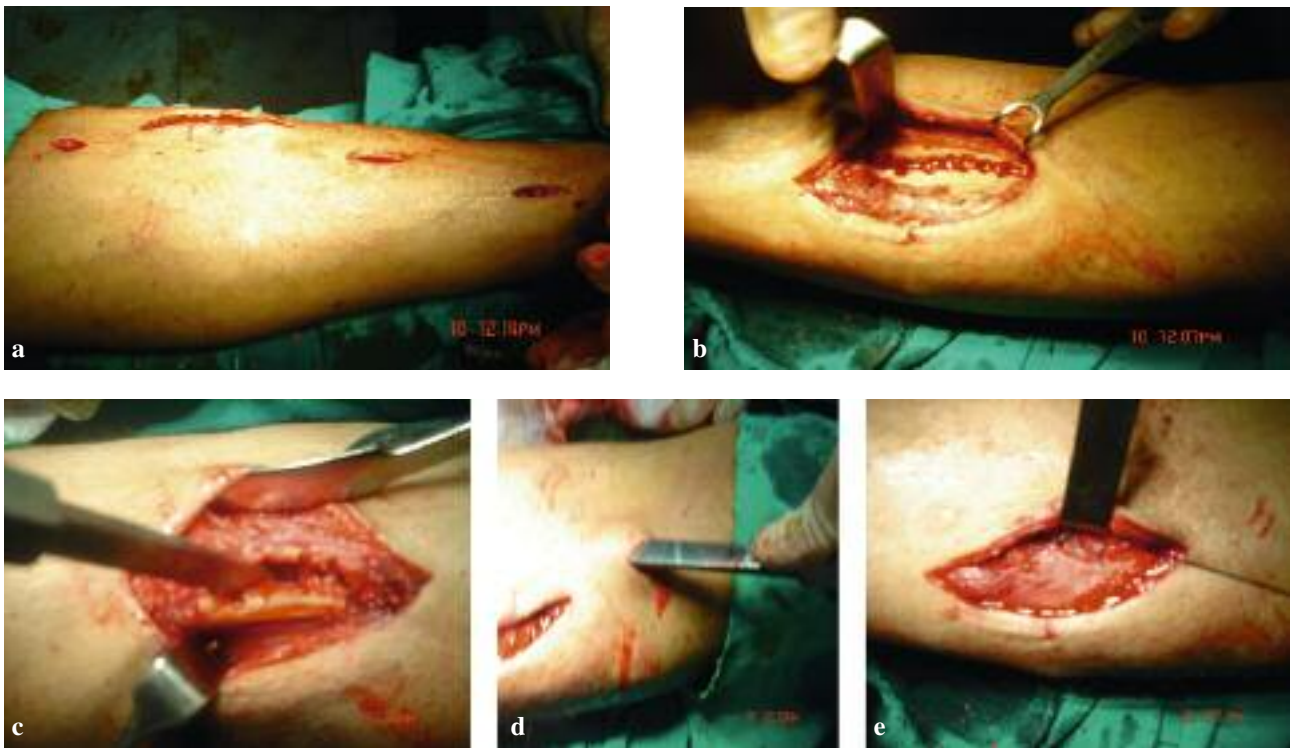

Fig. 1. — Consecutive steps in the procedure : (a) skin incisions ; (b)corticotomy site in the proximal tibia ; (c) osteoclasis of the posterior cortex with aid of osteotome ; (d) periosteal elevation with periosteal elevator ; (e) closure of the periosteum and soft tissue over the corticotomy site.

(13.9%) had a fair score and one patient (2.9%) had a poor score (table Id).

Patient satisfaction scores at the 12-month follow-up and at final follow-up ranged from 4 to 10 (mean ± SD : 7.1 ± 1.3) and 7 to 10 (mean ± SD : 8.7 ± 1.7) respectively.

Comparison of the pre- and post-operative QoL showed marked improvement with respect to pain ($p = 0.001$), emotional ($p = 0.001$) and social domains ($p = 0.001$) ; marginal improvement ($p = 0.05$) was noted in the mental health scale ($p < 0.05$) (table II).

The morbidity rate was 16.8%, corresponding to fracture of the tibia in one case (2.8%), wound ulcer in one (2.8%), haematoma in one (2.8%) and wound infection in two (5.8%). Only one patient (2.8%) required above-knee amputation because of a life-threatening secondary infection of his healing wound). There was no perioperative mortality.

The postoperative MRA study showed that all patients had acquired a new vascular leash, with collateral arteries and better visualization of the vessels.

DISCUSSION

Chronic critical lower limb ischaemia (CCLLI) represents microcirculatory dysfunction and impaired angiogenesis (*18*). Most CCLLI patients are unsuitable for surgery – revascularisation or angioplasty – and the current pharmacotherapy has limited effect (*11*).

Corticotomy and periosteal elevation improve vascularisation in patients with CCLLI through many pathways, first of all through induction of surgically controlled local persistent inflammation (*1*).

Once the inflammatory process has reached a critical surface / volume ratio, this induces

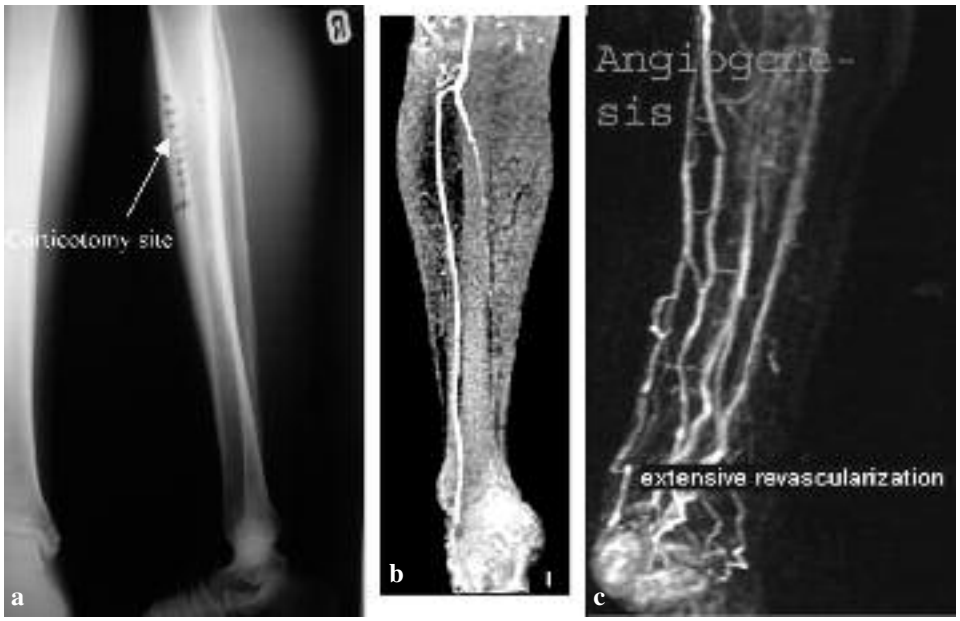

Fig. 2. — (a) plain radiograph showing the corticotomy site ; (b) Magnetic Resonance Angiography (MRA) study preoperatively showing occlusion of the posterior tibial artery, (c) four months MRA postoperative showing neovascularisation.

angioswitch (stage in which the inflammation develops its own microcirculation), resulting in the development of a bidirectional network of inflammatory neovascularisation (*10,25*). The triggering factors for angioproteins secretion in the inflammatory process are (i) inflammation hypoxia, (ii) plasma extravasation of kinins, (iii) direct production of angioproteins by macrophages (*24*) which stimulates the fibroblasts and endothelial cells to secrete angiogenic proteins (6,23). Angiogenesis sustains inflammation through several mechanisms : (i) O_2, nutrient supply and waste products removal, (ii) the new vessels are leaky, (iii) the endothelial cells express endothelial cell adhesive molecules (ECAM) which are inflammatory cells chemo attractants (*10,15*).

The second pathway is fracture dependent neoangeiogenesis through the inherent angiogenic power of the fracture haematoma, which is rich in both Vascular Endothelial Growth Factor (VEGF) and platelets (*22*). Platelets secrete platelet derived endothelial cell growth factor (PDECGF), which stimulates both microvessel remodelling and secretion of VEGF by osteoblasts (*21*). There is also a mobilisation of pluripotent cells from the bone marrow, which undergo a cascade differentiation resulting in formation of micro vessels (*5*). The fracture also increases the arteriolar shear stress, which causes endothelial cell phenotypic changes (*7*). Furthermore, the fracture induces enhanced haematopoietic function (*9*), resulting in increased local blood supply.

The third pathway is osteogenesis and angiogenesis coupling (*17*). The endothelial cell secretions (cytokines and growth factors) stimulate osteoblast secretion of VEGF and bone morphogenetic proteins, which stimulate osteogenesis and angiogenesis (*5*).

There is a possible fourth pathway which is neural dependent, as fine non-myelinated nerve fibres grow with neoangiogenesis (neurite extension – arborisation) secreting neuropeptites which facilitate inflammation and angiogenesis, and act as sensory innervation (*21*) ; this pathway still needs to be further investigated.

There is a fifth pathway : periosteal elevation induces a local inflammatory response with consequent inflammatory neovascularisation (*16*). Moreover stripping the periosteum interrupts its sensory nerve fibres (*9*), thus decreasing pain and

Table I. — Late results

		4th month		6th month		12th month		Final follow up	
		No	%	No	%	No	%	No	%
a- Ischaemic rest pain	Present	5	13.9						
	Absent	31	86.1						
b- Claudication pain	Absent	11	30.6			16	14.4	20	55.6
	Non-disabling	12	33.3			12	33.3	10	27.8
	Disabling	ss13	36.1			8	22.2	6	16.7
c- Wound healing	Healed	19	52.8	24	66.7	33	91.7	34	94.4
	Healing	11	30.6	10	27.8	1	2.8	0	0
	Resistant	6	16.7	2	5.6	1	2.8	1	2.8
	Recurrent	0	0	0	0	1	2.8	1	2.8
d- Overall Kelkar score	Excellent							20	55.6
	Good							10	27.8
	Fair							5	13.9
	Poor							1	2.9

Table II. — Quality of life

	Pre-op	post-op	p value
1. Emotional domain	33.4 ± 3.4	72.9 ± 9.4	0.0001
2. Limitation to social activity	28.5 ± 6.4	57.5 ± 9.8	< 0.05
3. Pain/anxiety domain	37.92 ± 6.51	74.56 ± 8.8	0.0001
4. Limitation to physical activity	51.3 ± 6.5	52.1 ± 6.6	> 0.05
5. Social domain	28.5 ± 6.4	57.5 ± 9.6	< 0.05
6. Physical domain	41.9 ± 5.7	44.7 ± 6.5	> 0.005
7. Vitality domain	35.4 ± 3.9	39.6 ± 6.1	> 0.05
8. General health domain	37.5 ± 4.1	39.7 ± 5.9	> 0.05
9. Physical health score	41.9 ± 6.5	42.1 ± 7.5	> 0.05
10. Mental health score	53.0 ± 6.4	57.9 ± 6.1	< 0.05
11. Overall score	46.4 ± 6.4	48.9 ± 7.1	0.05

Student's t-test was used (significance was set at $p \leq 0.05$).

facilitating ambulation, which also enhances vascularity through improved physical activity (*9*).

Many patients in this study presented with trophic skin lesions despite ASP above 50 mmHg, so the strongest indicator of failed collateral circulation and presence of CCLLI is the skin perfusion (*8*). The ASP did not change postoperatively as the current method did not open the arterial blockage, so the Rutherford *et al* (*20*) criteria for successful revascularisation procedures must be reconsidered.

In this study the immediate improvement in skin perfusion is attributed to inflammatory vasodilatation and the leaky nature of immature new vessels, and the immediate pain relief may be mostly related to stripping of periosteal nerves (*2*).

The current study demonstrated the effectiveness of the procedure, with respect to pain relief (ischaemic rest pain and claudication pain), wound healing and the global Kelkar score.

The procedure morbidity was not high. One diabetic patient required major amputation, likely due to the biologically compromised diabetic foot status. Diabetes has been shown to prevent new vascular leash remodelling due to PDECGF-B deficiency (*13*).

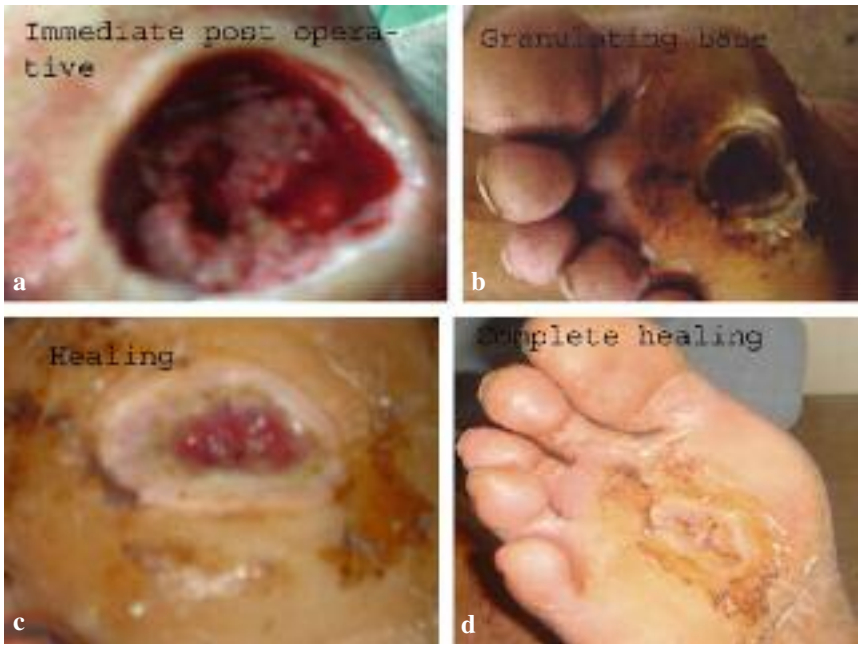

Fig. 3. — Plantar neuro-ischaemic ulcer. (a) plantar ulcer immediately postoperative ; (b) the ulcer with a granulating base ; (c) ulcer in healing stage ; (d) complete healing of the ulcer.

Compared with the high cost of surgical revascularisation (*14*) and the poor outcome of amputation (*3*), this procedure not only has a better cost benefit ratio but also it would not hamper surgical revascularisation if required later on.

Finally, the efficiency of the procedure was also documented radiologically, with demonstration of a new vascular leash, new collaterals and enhanced vasculature.

In conclusion, this procedure appears as a valuable tool, which should be evaluated in randomised studies for management of CCLLI, as it appears to be safe, efficient and effective in terms of improvement of quality of life. The findings of this study also support the opinion of Street *et al* (*22*) that fracture haematoma is angiogenic.

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