Improvement in Blood Supply After “Heparin-Dextran” Therapy in Patients of Buerger’s Disease with Critical Limb Ischemia

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Received: 15 September 2010 / Accepted: 31 May 2012 / Published online: 19 June 2012
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Abstract Alleviating the agonizing pain of critical limb ischemia (CLI) in patients of Buerger’s disease (BD) has been challenging, due to lack of definitive treatment; “Heparin-Dextran” infusion has been tried in this study. Assessment of clinical improvement and vascular changes following therapy. Patients with CLI admitted to emergency surgical ward were studied prospectively. BD was diagnosed by Shionoya’s criteria, and confirmed by digital subtraction angiography (DSA). Heparin and Dextran intravenous infusion was administered for 10 days. Severity of rest pain, ischemic changes in the feet, claudication distance and ankle brachial index (ABI) were estimated prior to therapy, at completion and 3 weeks after therapy. Vascular changes were assessed by CT angiography (CTA) performed

prior to and 3 weeks after therapy. Twenty consecutive patients were studied. Successful hemodilution reflected by decreased hematocrit (37.4 % to 32.6 %, $p<0.05$) and increased mean ABI (0.46 to 0.83, $p<0.01$), improved rest pain in 75 % patients ($p<0.001$), increased claudication distance in 94 % ($p<0.05$) and ulcers healing in 70 % patients. CTA revealed recanalised vessels (decreased length of occluded segments) in 10 (50 %, $p=0.005$), increased collaterals in 12 (60 %, $p<0.01$) and improved distal run-off in 13 (65 %, $p<0.01$) patients. “Heparin-Dextran” therapy in patients of CLI from BD improves tissue perfusion by increasing collaterals and recanalisation of vessels, resulting in significant relief from rest pain and clinical improvements. CTA is as efficacious as DSA for evaluation of BD.

NB The study was presented at the 6th International Congress of Asian Vascular Society and 11th Annual Conference of Vascular Society of India, Bangalore, 5th November, 2004. (Paper presentation)

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Keywords Buerger’s disease · Critical limb ischemia · Heparin-Dextran · Angiography

Introduction

Buerger’s disease (BD) is a segmental inflammatory obliterative disease of obscure etiology, affecting small and medium-sized vessels, producing ischemia and gangrene of extremities [1]. Being more prevalent in Eastern Europe, Mediterranean, and Asian countries, BD is the commonest peripheral vascular disease (PVD) in young patients (45–63 % of PVD) in India, affecting young smokers [2–4].

Tobacco abuse has been attributed to play a major role in initiation and progression of the disease. Other factors such as genetic predisposition, immunologic mechanisms, endothelial dysfunction, and coagulation abnormality may have some role in pathogenesis and manifestations of BD [2–5].

Mainstay of diagnosis is clinical, as outlined by Shionoya [6]. Characteristic finding on digital subtraction angiography (DSA) confirms the clinical diagnosis of BD, but is invasive and has risk of contrast and procedure-related complications [1, 7]. Computed tomographic angiography (CTA), a noninvasive imaging tool, has efficacy similar to DSA for imaging of large and medium vessels [8, 9].

The first line of treatment is conservative. Cessation of tobacco use is widely accepted and cornerstone of therapy [2–4]. Pharmacologic agents and many surgical procedures have shown some benefits in different series [10–16]. None of the treatment modality has produced promising success, and the definitive therapy for BD is yet to be search for [16]. Nonsurgical treatments seem to be more advantageous and perhaps more successful than surgical procedures, and are replacing the surgical techniques [14, 16].

Angiogenic stem cell therapy is potentially promising, but is not suitable or immediately effective for relief of agonizing rest pain of critical limb ischemia (CLI) [16–20]. Anticoagulants, thrombolytic and antiplatelet drugs have shown favorable results for treatment of BD in some studies [21–23]. Heparin has shown stimulatory effect on angiogenesis in vitro although translation into clinical effects remains to be evaluated [24–26]. Hemodilution therapy may be useful for treatment of CLI by virtue of its volume expansion and rheological properties [27–29].

Besides anticoagulants and hemodilution, no other treatment modality is suitable for early and effective control of severe rest pain in CLI. In this context we have administered “heparin and dextran” combination therapy in patients of BD with severe rest pain, and objectively assessed clinical improvement as well as vascular changes by CTA.

Patients and Methods

Male patients of CLI, younger than 50 years, admitted to the emergency surgical ward, from July 2002 to November 2003, were consecutively enrolled into this prospective cohort study. All of them were chronic smokers and satisfied Shionoya's clinical criteria [6]. The diagnosis was confirmed by characteristic findings on DSA.

The research protocol and permission for DSA was approved by the institute's ethical committee. Informed consent in prescribed forms was taken from all patients for DSA and for enrolment into the study voluntarily, after explaining the purpose of the study, procedure details, and the options to quit at their will.

Severity of rest pain was estimated by point numerical rating scale (NRS 101 [30]). Extents of ischemic ulcers, gangrene, or pregangrenous changes, claudication

distance and ankle brachial index (ABI) were assessed at the outset. Laboratory tests for blood sugar, lipid profile, renal function, hemogram with hematocrit, and investigations for thrombotic disorders such as coagulation study, protein C and S, antithrombin III, lupus anticoagulant, rheumatoid factor, and antiphospholipid antibody were obtained.

DSA and CTA of lower limbs were performed in all patients to note sites and length of narrowing/occlusions, flow patterns (if not completely occluded), reformation by collaterals, and distal runoff (Fig. 1a and b).

Patients were advised for abstinence from smoking. Care of feet included cleaning and keeping them dry, antiseptic dressing of ulcers. Injection heparin and dextran-40 (500 ml over 24 h) infusion was administered for 10 days. Heparin (unfractionated) was given as 80 IU/kg intravenous bolus, followed by 18 IU/kg/h continuous intravenous infusion, titrating dose according to targeted aPTT 70–90 s.

The patients were asked to quantify their pain using 101-point numerical rating scale (NRS-10130) “assuming 100 as most severe unbearable pain.” Analgesic was administered on demand, and was taken as an objective assessment of pain relief.

Clinical assessment was repeated after 10th day and 3 weeks, with repeat CTA after 3 weeks.

Statistical Analysis

Statistical analyses of data were carried out using SPSS version 16 software.

Paired *t*-test was used to compare numerical data and Pearson's correlation to correlate CTA and DSA findings. Baseline clinical and CTA parameters were compared to those after therapy by Wilcoxon signed-rank test. A *P* value of <0.05 was considered significant.

Results

Twenty consecutive male patients of BD with CLI, aged 20–50 (mean 40.25) years, were studied. All were chronic smokers of duration 2–35 (mean 17.85) years: 14 (70 %) patients presented with the first episode of CLI, 4 (20 %) patients with the second, and 4 (10 %) patients with third episode, after an interval of 6–12 months.

All had rest pain in the feet, with bilateral limb involvement in 2 patients. Following therapy rest pain was relieved completely in 15 (75 %, *P*<0.01) patients and partially in 5 (25 %). Record of pain scores showed significant reduction by 6 days through end of therapy (Tables 1 and 2, *P*<0.001), and persisted beyond 3 weeks following therapy (Fig. 2).

Fig. 1 Upper panel—**a** DSA of a patient showing occlusion of left femoropopliteal artery (white arrow, partial occlusion; red arrow, complete block); **b** network of minute corkscrew collaterals (white arrows), without reformation of distal vessels; lower panel—**c** CTA of a patient showing 12.42 cm thrombosed segment of femoropopliteal artery, without significant collateral and poor distal runoff; **d** CTA 3 weeks after therapy in the same patient, showing partial recanalization (occluded segment 4.89 cm), with increased collaterals and improved distal runoff

None had recurrence of rest pain or CLI during 6-month follow-up.

Eighteen (90 %) patients had claudication with mean claudication distance of 101.39 m at presentation, which improved in 17 (94 %) patients to 214.44 m after 10 days and 310.00 m after 3 weeks ($P<0.05$).

Ulcers on toes were noted in 14 (70 %) patients. Following the therapy and daily dressing, ulcers healed in 6 (42.85 %) patients and showed signs of healing in other 4 (28.58 %) patients; thus, limb salvage was achieved in 70 % of patients. Worsening of ischemic ulcers and gangrene required amputation in 4 (28.58 %) patients.

ABI was calculated with handheld Doppler in 14 patients, before and after treatment; in others patients, complete occlusion of femoropopliteal and calf vessels precluded Doppler recording. Adequate hemodilution (decreased

mean hematocrit 37.4–32.6 %, $P<0.05$) resulted in significant improvement in ABI (mean 0.46–0.83, $P<0.001$).

In this study, 256 arterial segments were studied by angiography. Stenosis and/or occlusion were noted in 102 segments by DSA and 98 segments by CTA (pickup rate 96.7 %). Sites and length of occlusion, number and size of collaterals, and reformation of distal vessels as on DSA were well correlated with that on CTA. These parameters on CTA were compared before and after therapy.

The sites of occlusion in different arteries were categorized and compared separately. Length of occluded arterial segments decreased from a sum of 550 cm before therapy to 391 cm after therapy, thus recanalized by 159 cm (mean 7.95 cm) (Fig. 1c and d).

Significantly increased reformation of distal arteries on post-therapy CTA was noted in 10 (50 %, $t=3.204$, $P=0.005$) patients. Collaterals were graded according to

Table 1 Intensity of rest pain (NRS – 101 score) of individual patients

Sr. No. of Patients	Day 1	Day 10	Day 21
1	100	10	15
2	40	00	00
3	90	10	20
4	100	30	15
5	80	20	20
6	100	07	10
7	100	20	25
8	90	10	10
9	80	10	15
10	95	10	10
11	100	80	60
12	100	20	50
13	75	10	20
14	95	30	50
15	90	05	10
16	90	70	50
17	95	40	60
18	100	70	85
19	100	30	50
20	90	70	40
Mean	90.50	29.00	31.25

't' value: t_1 -12.799, t_2 -13.066, $p < 0.01$

the number and size; an increased number of collaterals were found in 12 (60 %, $P < 0.001$) patients and distal runoff in 13 (65 %, $P < 0.01$) patients after treatment (Fig. 1d).

This study documents increased blood flow beyond the occluded segments after "heparin–dextran" combination therapy as demonstrated by CTA. The overall clinical improvement in 10 (50 %) patients and improved vascular changes in 13 (65 %) patients were well correlated (Fig. 3).

Table 2 Changes in Pain Intensity (mean NRS score) with duration of therapy

Day of therapy	Mean NRS score	<i>t</i> -value	<i>P</i> value
1	90.50		NS
2	85.00	5.08	
3	76.75	8.50	
4	71.25	9.48	
5	62.50	9.40	$P < 0.001$
6	54.00	10.31	
7	45.50	11.56	
8	38.00	11.08	
9	38.85	12.50	
10	29.00	12.79	
Day 21 (Post-therapy)	31.25	13.06	

$p < 0.001$ (significant); NS – Non Significant

Histopathology study of arteries from amputated feet ($n=04$) revealed inflammatory thrombus, panangiitis, and sparing of internal elastic lamina, suggestive of BD.

Discussion

Abstinence from smoking and conservative measures such as analgesics, antiplatelet, foot care, physiotherapy, and exercise are the first line of treatment for BD, but they provide temporary symptomatic relief without effect on disease modification [2–4, 14, 16].

Aspirin, pentoxifylline, prostacyclins, and VEGF are worth trying in patients with stable disease for prevention of acute episodes of CLI [10–12]. Surgical procedures such as omental transfer and sympathectomy have been temporarily effective in some patients [13–15]. Sympathectomy confers partial and temporary response, with up to 45 % recurrence without affecting amputation rate [14]. Arterial reconstruction and bypass grafting are technically difficult due to multisegmental and calf vessel occlusion, and have increased risk of graft occlusion [15, 16].

Heparin in patients with acute thromboembolic episodes prevents propagation of thrombus and maintains patency of collateral vessels [21]. This is the first study in English literature, evaluating the role of anticoagulant and hemodilution combination for BD.

Two Russian studies have described improved microcirculation following regional infusion of anticoagulants and thrombolytic therapy for treatment of acute episodes of BD, with the goal of long-term limb salvage.

Gervaziev et al. [22] have described immediate and long-term results of intra-arterial infusion of fibrinolysis activators and microcrystal suspensions (hydrocortisone, oxytetracycline, zinc insulin) in patients of thromboangiitis of lower limbs. Lysis of fresh thrombi was noted in 2/13 (15 %) patients. In patients with chronic arterial insufficiency ($n=60$), arrest of ischemia was noted, with limb preservation up to 2 years, in 92.5 %.

In another study by Bykov et al. [23], intra-arterial infusion of heparin alone did not eliminate blockade in chronic ischemic limbs. But regional thrombolysis followed by microcrystalline (anti-inflammatory and immunosuppressive agents) infusion improved microcirculation and lowered amputation rate.

Although heparin has shown stimulatory effects on angiogenesis in vitro, its translation into clinical effects remains to be proved [24–26].

Dextran-40, a polysaccharide plasma volume expander, has been used for hemodilution, for treatment of chronic limb ischemia [27–29]. Decreasing viscosity and rouleaux formation prevent slugging of small vessels and capillaries. Overall effects of volume expansion, rheological and anti-

Fig. 2 Graphical presentation: decreasing intensity of rest pain (mean NRS score) with “heparin–dextran” therapy

platelet actions of Dextran, improves microcirculation and help in ulcer healing.

In our study, adequate hemodilution as indicated by decreased hematocrit from 37.4 to 32.6 % ($P<0.05$) resulted in significant increase in mean ABI from 0.46 to 0.83 ($P<0.05$) and mean claudication distance from 101.39 to 310.00 m ($P<0.01$).

Heparin infusion, along with dextran, showed significant improvement in microcirculation with relief from rest pain (75 %) and ulcer healing in 70 % patients. Stem cells are novel therapy stimulating neoangiogenesis to improve circulation in the ischemic limbs. Therapeutic angiogenesis with stem cells, although potentially promising for treatment of BD, is still at an early stage and limited to clinical trials [16–20].

In a preliminary safety and efficacy study by Motukuru et al. [17], autologous bone marrow mononuclear cells injected into calf muscles of patients with BD resulted in effective ulcer healing, increased ABI, and improved

transcutaneous oximetry, with limb salvage till 6 months in 33 of 36 patients. A review of total 18 clinical studies in English literature overviews the demonstrated safety and promising efficacy of autologous stem cells therapy for BD [18]. The long-term benefit of therapy is found to be extended up to 2 years in another study by Matoba et al. [19].

This novel therapy is not without complications [20]. Neoangiogenesis may take place a few weeks after injection of stem cells, so clinical effects may be delayed, incomplete and inadequate. Thus, stem cell therapy may not be suitable or effective for immediate relief of agonizing rest pain.

In our opinion “heparin–dextran” combined therapy has a significant role in the alleviation of agonizing rest pain, increasing claudication distance and healing of ischemic ulcers in patients of BD. Although this study encompassed a small cohort of 20 patients, none of the patients developed recurrence during follow-up of 1–5 years (mean 3.6 years), thus showing excellent long-term results. Further studies on more number of patients, in comparison model with longer

Fig. 3 A bar chart showing correlation of clinical and CTA improvements after therapy

follow-up, would define the role of this therapy for the long-term management of BD.

A few authors have described improvement in microcirculation after treatment of CLI, as measured by DSA [17], Doppler [27, 28], plethysmography [29], thallium scintigraphy, or RBC scan. In this preliminary study, CTA, a noninvasive imaging tool, has been used for assessment of vascular changes, with efficacy for vascular imaging, similar to DSA. CTA findings of increased blood flow are correlated with clinical improvement (Fig. 3).

Limitation of the Study

Although temporary remission with conservative measures is known in BD, most of such patients recur with severe symptoms sometimes later [2–4, 14, 16]. However, studying their effects on neoangiogenesis in a control fashion could have better clarified the role of heparin–dextran therapy in CLI.

A control arm could not be added to the study protocol because active treatment could not have been denied to any patient of CLI having agonizing rest pain, also because getting an invasive DSA and expensive CTA in a patient without therapeutic intervention was not cleared by the ethical committee. Thus, it remained a small case series only, but its importance lies in being a preliminary study showing the definitive radiological evidence of neoangiogenesis.

Conclusions

“Heparin–dextran” combination therapy in BD with CLI effectively improves microcirculation, resulting in alleviation of agonizing rest pain, increasing claudication distance, and healing of ischemic ulcers. This therapy is special over other treatment modalities including stem cells, by being most effective for immediate relief from rest pain. Larger controlled studies comparing the effects of this therapy with conservative management as well as with other treatment modalities, and with longer follow-up, would define its therapeutic role in the long-term management of CLI from BD.

Efficacy-wise CTA is comparable to DSA, and being noninvasive is preferable for vascular imaging in BD.

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