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Thromboangiitis obliterans: Aggressive angioplasty provides a potential solution (randomized pilot study)

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Abstract

Background: Thromboangiitis obliterans is an inflammatory disease affecting both medium- and small-sized vessels. Vasodilators, antiplatelets were proposed for treatment but the effect was minimal.

Objective: This study was conducted to investigate the effect of balloon angioplasty on patients with Buerger's disease compared to medical treatment.

Methods: Between January 2006 and December 2016, 82 patients with Buerger's disease were enrolled in the study, of whom 52 were randomized to the aggressive endovascular intervention and 30 were randomized medically by cilostazol and aspirin as a control group. In all, 23% of the patients presented with severe claudication, 50% with ischemic rest pain and 27% with ischemic ulcers. Randomization was done using the opaque envelope method. Allocation concealment was maintained to ensure no selection bias. Patient groups were compared for the duration of ulcer healing, ankle–brachial index, peak systolic velocity changes and transcutaneous oximetry (TcPO2) level for 30 months.

Results: No major procedural complications occurred in the endovascular group. Angiographic success was achieved in 100% of supragenicular lesions but in 90% of infrapopliteal lesions. The endovascular group showed a statistically significant improvement in the ulcer healing size and duration at 6 months after the procedure with a mean time of 3 ± 0.9 months compared to 5.8 ± 1.69 months for the medical treatment group ($p < 0.001$), the mean TcPO2 from 27.23 ± 16.75 mm Hg (range: 0–56 mm Hg) before the procedure to 71.32 ± 12.94 mm Hg (range: 52–92 mm Hg) following revascularization ($p < 0.01$). The mean ankle–brachial index significantly improved from 0.54 ± 0.14 preoperatively to 0.82 ± 0.08 at final follow-up ($p < 0.01$).

Conclusion: The endovascular therapy should be considered as an effective, safe, minimally invasive method in the light of the promising results after a modification of the standard technique.

Keywords

Buerger, angioplasty, aggressive

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Introduction

Buerger's disease is a non-atherosclerotic disease, where its pathology is mainly inflammation and thrombosis with a segmental distribution. According to vascular experts specializing in this disease, diagnostic criteria are as follows: age less than 45 years; a current or recent smoker; the presence of distal extremity ischemia; excluding any hypercoagulable states, autoimmune diseases, diabetes mellitus; any proximal source of emboli; and angiographic findings consistent with the condition in the clinically affected and non-affected limbs.[1] It mainly affects small- and medium-sized neurovascular bundle[2] in young male patients who are smoking heavily.[3] This vascular disorder is more common in the developing countries of Asia, the Middle East and Eastern Europe. Thus, there is likely to be an increasing number of patients with critical limb ischemia due to Buerger's disease in developing countries. However, no established remedy exists for Buerger's disease other than discontinuation of cigarette smoking to

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Table 1. Diagnostic criteria for atypical thromboangiitis oblitrans.

- Smoking history
- Onset before the age of 50
- Partial infrapopliteal arterial occlusions
- Iliac and/or superficial femoral artery involvement
- Either upper limb involvement or phlebitis migrans
- Absence of atherosclerotic risk factors (such as hypertension, diabetes mellitus, hyperlipidemia or cardiovascular disease) other than smoking.
- Exclusion of other vasculitis or hypercoagulable states by investigations for rheumatoid factor and lupus anticoagulants or serologic investigations

prevent disease progression and avoid major amputation. Typically, the disease usually starts in distal small vessels; however, it has been reported that iliac and femoral arteries are also affected in 25% and 6.8%, respectively.[4–6] Although smoking cessation has proven to reduce the risk of amputation in Buerger's disease, several forms of treatments were used, but the results were discouraging.[7] Surgical revascularization was ineffective due to distal vessel disease;[6,8] other options like prostaglandins,[9] thrombolytic, calcium channel blockers,[10] anticoagulation, sympathectomy,[11] adrenalectomy and spinal cord stimulation[12] were used, but the outcome was unrewarding. Omental transfers[13] and stem cell treatment[14] have all been tried with limited success in reducing rest pain and evading amputation. Considering these limitations, angioplasty was considered as an alternative method of treatment of Buerger's disease (Table 1).[15,16]

The objective of this study was aimed to verify the effect of angioplasty on the clinical outcome of patients with Buerger's disease compared to those treated conservatively and its impact on the reduction of amputation rate.

Materials and methods

A randomized pilot study was designed to explore the endovascular therapy as a modality for treating acute critical limb ischemia in patients with Buerger's disease. Simple randomization was done using the opaque envelope method, which was done and recorded by the principal investigator. Allocation concealment was maintained to ensure no selection bias.

After getting approval of our institutional review board (IRB) (number R.18.05.187) after exclusion of all other causes such as hypercoagulable state, proximal embolization, vasculitis or peripheral artery disease (PAD), 109 patients were diagnosed with Buerger's disease. After explaining the nature of the disease and the proposed treatment options including the benefits and side effects associated, 27 patients refused to be randomized and preferred to receive endovascular treatment; all patients stopped smoking before enrollment into the trial (Figure 1). Consent was verbally taken and documented on the patient file with the patient's signature during the clinic appointment and again was reviewed with the patient immediately before the start of the procedure. A total of 82 patients with Buerger's disease were treated either by angioplasty (group A, 52 patients, 63.4%) or conservatively with aspirin and cilostazol (group B, 30 patients, 36.6%) from January 2006 to December 2016. In all, 43 patients (89%) in group A showed infrapopliteal occlusion, while 9 patients (11%) proved to have infra as well as supragenicular lesions (femorocrural lesions) affecting the superficial femoral artery (SFA) (7 patients) and iliac arteries (2 patients) or combined in 5 patients.

Computed tomographic angiography (CTA) was used to delineate the disease site and its approximate length, any calcification if present, also the shape and site of corkscrew collaterals and the presence of any distal run-off vessels.

Ipsilateral access was used in cases of isolated infragenicular involvement. In contrast, contralateral access with crossover method was used in supragenicular lesions, especially those involving the external iliac artery (EIA) or SFA with no stump for sheath placement. Heparin was administered through the 6F sheath (Cook, Bloomington, IN, USA), access sheath at a dose of 100 IU/kg. The arterial tree was visualized under fluoroscopy by injecting dye through the access sheath. We used the loop technique with the 0.035-in. hydrophilic J-tip guidewire (J-tip; Terumo Corporation, Tokyo, Japan) and a supporting 4-Fr multipurpose catheter to cross the lesions; 0.014 in./0.018 in. (V-18, V-14 ControlWire Guidewire; Boston Scientific, Marlborough, MA, USA) was used to tackle tibial vessels to cross the occlusion using the same technique if possible. Still, mostly the wire will cross using a supporting catheter such as the TrailBlazer Support Catheter (Medtronic, Minneapolis, MN, USA). The occlusive lesions were serially dilated with a succession of balloon catheters starting with $2.0 \times 20\,mm^2$ and incrementally processed to larger sizes. A modified technique was used where dilatation was done through an antegrade approach progressing sequentially distally with a gradual elevation of the pressure up to 18 ATM, which was maintained for up to 10 min. The balloon diameter (Admiral Xtreme™; Medtronic) used was chosen according to the angiographic diameter of the healthy artery above and below the lesion; incremental diameters were used to achieve the desired lumen size if compared to the normal artery adjacent to the treated segment. Sizes for balloons used to treat supra-inguinal arteries were ranging from 4 to 8 mm in diameter. For infra-inguinal arteries, balloon sizes ranging from 4 mm to up to 6 mm in diameters were used. For infragenicular arteries, sizes ranging from 1.5 to 3 mm were used to achieve a successful angioplasty. All lesions were managed with percutaneous transluminal angioplasty (PTA) alone, and no stent deployment was required to restore patency in any of the cases. Recommendations of both the International Society for Cardiovascular Surgery and the Society for Vascular Surgery were followed to evaluate an initial success;[17,18] immediate angiographic success was considered if we could establish a

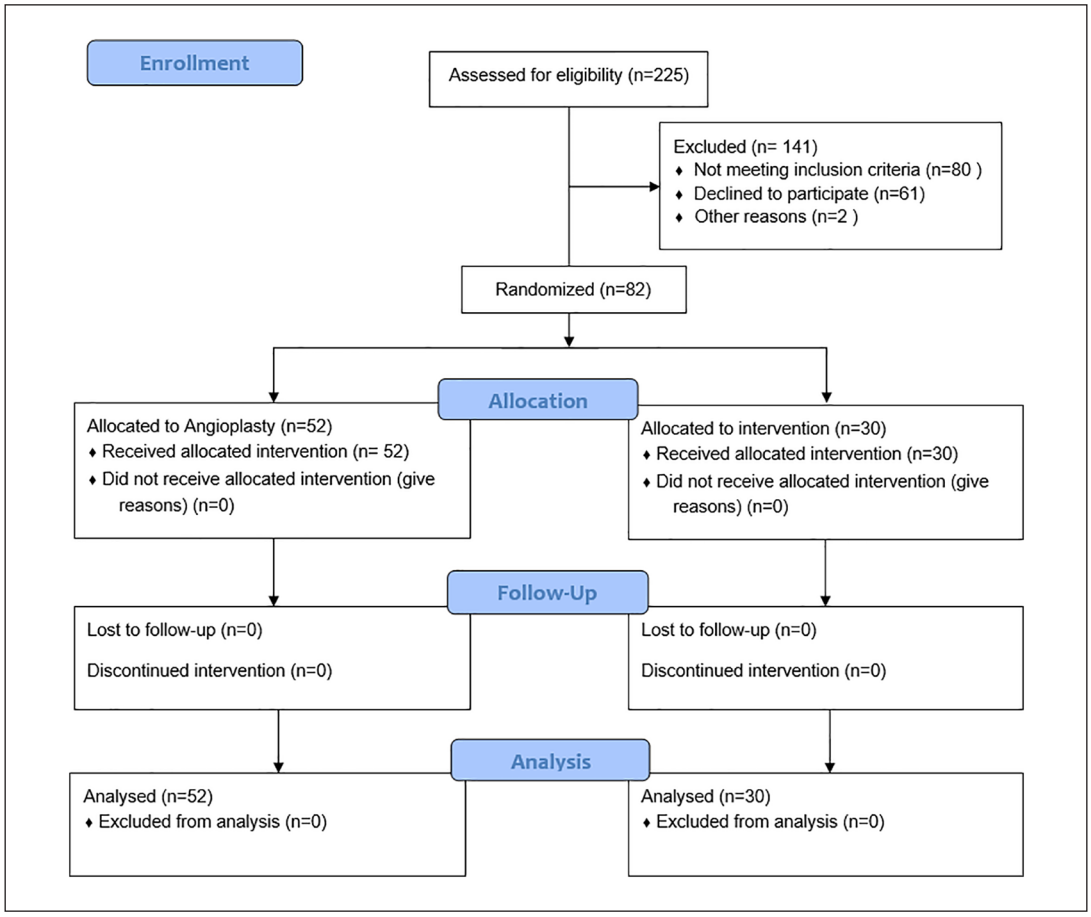

Figure 1. A CONSORT flow diagram for the study process.

flow to foot arch arteries with residual stenosis of less than 30%. The proposed clinical success depends on the improvement of Rutherford classification for at least one category or healing of an ulcer, improved claudication distance and resting pain;[19] this was also documented by an increase in ankle–brachial index (ABI).[20] If indicated, patency was checked by color Doppler scan or CTA if needed. Duplex criterion for restenosis was an increase in the peak systolic velocity for more than 2.4-fold. Postoperatively, patients were discharged from the hospital on dual antiplatelets of aspirin (100 mg/day) and clopidogrel (75 mg/day). The latter was maintained for 3 months and then stopped.

Clinical assessment and Doppler ultrasound were done immediately before patient discharge; at the first, third and sixth months after the procedure; and yearly afterward.

Differences in ABI,[20] TcPO2,[21] and Rutherford category[22] data between before and after intervention were analyzed using the signed-rank test for non-parametric data (Wilcoxon test). The data were considered statistically significant if $p < 0.05$.

In this pilot study, we wanted to test the trial procedure and process so that we can provide a proof for the subsequent main trial. As the study was designed to compare two groups, we used rules of thumb to estimate the sample size for this trial. Browne[23] cited the use of 30 patients or greater to study a parameter. Julious[24] used 12 patients as a minimum. Teare et al.[25] recommended 70 subjects to increase the precision of the standard deviation. So, we decided to go with more than 70 cases to reduce type 1 error 5%, at the Power $1-ß$ of 80%

Results

All patients were male (mean age: 32.4 ± 6.6 years; range: 21–42 years) and fulfilled the clinical criteria mentioned by Shionoya et al.[4] for Buerger's disease[1]. All patients were not exposed to any surgical or endovascular intervention before to improve their limb circulation. Patients enrolled in the endovascular group presented by severe claudication ($n=12$, Rutherford class III), ischemic rest pain ($n=26$, Rutherford class IV) and ischemic ulcer and minor tissue loss ($n=14$, Rutherford class V). Demographic characteristics such as age did not show any significant difference between both groups (Tables 2 and 3).

CTA showed only a single-vessel run-off in 50 (61%) patients and two-vessel run-off in 17 (20.7%) patients. None of the infrapopliteal vessels was in linear continuity with the

Table 2. Comorbidities and demographic difference between groups.

	Medical treatment		Angioplasty		p value
	Yes	No	Yes	No	
Coronary artery disease	5	25	6	46	0.367
Hypertension	7	23	6	46	0.137
Diabetes	3	27	2	50	0.255
Age (mean ± SD)	33.03 ± 0.54		32.15 ± 0.54		0.567
ABI before treatment (mean ± SD)	0.54 ± 0.15		0.55 ± 0.14		0.955

SD: standard deviation; ABI: ankle–brachial index.

Table 3. Disease severity before intervention.

			Intervention type		p value
			Medical treatment	Angioplasty	
Rutherford grade	Severe claudication	Count	6	12	0.178
		% within	33.3%	66.7%	
	Ischemic rest pain	Count	10	26	
		% within	27.8%	72.2%	
	Minor tissue loss	Count	14	14	
		% within	50.0%	50.0%	
Total		Count	30	52	
		% within	36.6%	63.4%	

pedal or arch vessels. In 15 (18.3%) patients, no run-off but only collaterals below the tibioperoneal trunk were detectable. Together with the infrapopliteal disease (nine patients), there was a disease affecting the supra-popliteal arteries which were concurrently present in the EIA and SFA in five patients, and it was only present in the SFA alone in seven patients. Nearly all cases had a combined arterial affection, but for quantification, SFA was treated in 9 patients, iliac vessels were treated in 5 patients, the ATA artery was treated in 34 patients, PTA was treated in 28 patients and peroneal was treated in 26 patients.

Angiographic findings of corkscrew collaterals were around the diseased vessel in all patients; these collaterals were mainly types III and IV in patients with supragenicular involvement, or types I and II in patients with infrapopliteal involvement (Figure 2 and Table 4).[26,27]

After successful recanalization, the number of corkscrew collaterals was reduced dramatically, and sometimes no collaterals could be detected or any sluggish flow (Figures 2 and 3).

All supragenicular lesions were successfully recanalized without residual stenosis or dissection, and the final angiogram showed reestablishment of flow to the popliteal territory. Technical success was achieved in 47 (90.4%) patients with infrapopliteal lesions. Straight-line flow to the arch vessels was established in three arteries in 19.2% (n=9/47) of the cases, in two arteries in 51% (n=24/47) and one artery in 29.8% (n=14/47).

The failure of the technique 9.6 % (n=5) was either due to difficulty crossing the lesions or presence of additive thrombotic lesions.

There was a continuous line flow into at least one crural vessel supplying the foot arch vessels; sometimes, there was a successful recanalization of two or three vessels down to the arch. The anterior tibial artery was the primary vessel supplying flow to the pedal arch in 5.8% (n=3/52) of the successfully revascularized vessels. In comparison, the peroneal and posterior tibial arteries were dominant in 5.8% (n=3/52) and 13.5% (n=7/52), respectively. Two vessels were supplying the foot arch as in ATA and PTA in 17.3% (n=9/52) patients, PTA with the peroneal artery in 11.5% (n=6/52) patients and ATA and peroneal in 19.2% (n=10/52) patients. Three-vessel run-off to the arch was in 17.3% (n=9/52) patients. All patients were followed for an average of 60 ± 8.1 months (range: 45–70). The clinical status of the endovascular group showed improvement by an average of 2.9 ± 0.96 months. Rutherford categories ranged from 2 to 3 ($p < 0.001$). Ischemic ulcers in the angioplasty group completely healed at 6 months after the procedure with a mean time of 3 ± 0.9 months compared to 5.8 ± 1.69 months for the conservative treatment group ($p < 0.001$). No recurrence of these ischemic ulcers was detected, and there were no major amputations but only toe amputation in eight of the patients. There was a statistically significant improvement in the mean TcPO2 from 27.23 ± 16.75 mm Hg (range: 0–56 mm Hg) before the

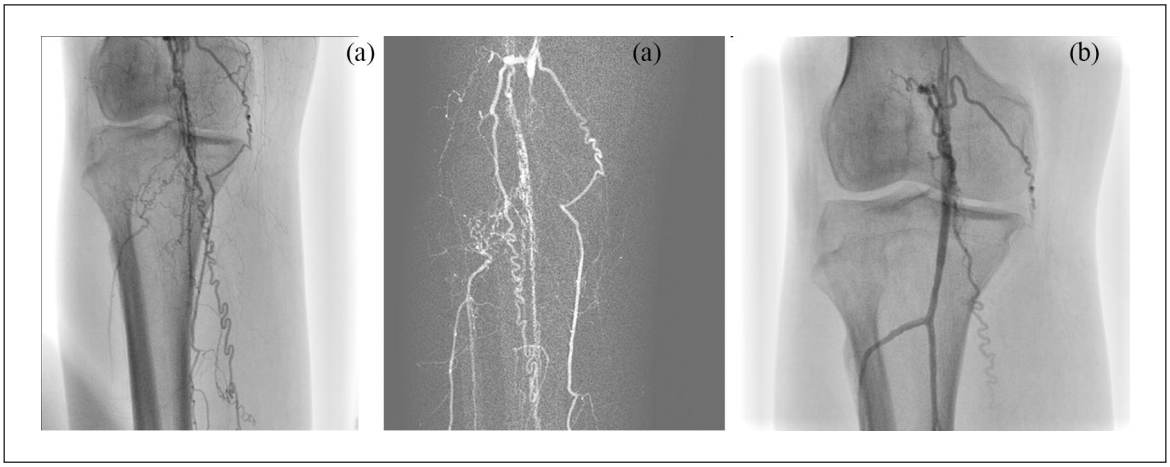

Figure 2. (a) Corkscrew collaterals around the popliteal artery (types I and II) and (b) collaterals burden was dramatically reduced after restoring the tibial flow.

Table 4. Classification of corkscrew collaterals.[13]

Type I	Artery diameter > 2 mm, large helical sign
Type II	Diameter > 1.5 mm and ⩽ 2 mm, medium helical sign
Type III	Diameter > 1 mm and ⩽ 1.5 mm, small helical sign
Type IV	Diameter < 1 mm, tiny helical sign

procedure to 71.32 ± 12.94 mm Hg (range: 52–92 mm Hg) following revascularization ($p < 0.01$). The mean ABI significantly improved from 0.54 ± 0.14 preoperatively to 0.82 ± 0.08 at final follow-up ($p < 0.01$).

Four patients (50%) in the supragenicular group and eight (18.2%) in the infrapopliteal cohort showed restenosis detected by duplex at 24 months. Different levels of restenosis detected. One patient had iliac-level stenosis, one patient had SFA stenosis, three patients with ATA stenosis, one patient PTA stenosis, one patient peroneal stenosis, ATA and peroneal in one patient, ATA and PTA in one patient, PTA and peroneal in two patients SFA and ATA in one patient; however, none of these patients needed re-intervention as they were asymptomatic and showed no evidence of ulcer recurrence.

Kaplan–Meier analysis comparing survival for both the medical treatment group and the angioplasty group also found that participants undergoing angioplasty had a longer median time to amputation (18 months; 95% confidence interval (CI): 15.2–20.8 months) compared to the groups receiving medical treatment only (14 months; 95% CI: 7.5–20.5 months). The percentage of censored cases present in the angioplasty (84.6%) and medical treatment group (53.3%) was not similar.

By comparing ankle–brachial pressure index (ABPI) before and after intervention for both medical and angioplasty groups, in the medical treatment group, before the treatment mean was 0.54 ± 0.15 (ranging from 0.25 to 0.8) and after the treatment mean was 0.78 ± 0.12 (ranging from 0.45 to 0.97), while ABPI in the angioplasty group before intervention mean was 0.55 ± 0.14 (ranging from 0.3 to 0.8) and after angioplasty mean was 0.83 ± 0.083 (ranging from 0.67 to 0.96).

By comparing tissue O2 tension in both groups, the mean before the intervention in the medical group was 27.7 ± 20.62, and after treatment, the mean was 43.47 ± 17.55, while in the angioplasty group, the TcPO2 mean before the intervention was 27.23 ± 16.75, and after angioplasty, the mean was 71.15 ± 13.08.

We compared the mean of both groups before and after the intervention. In the medical treatment group, ABPI mean increased by 0.235 (95% CI: 0.16–0.31) compared to pretreatment, while in the angioplasty group, ABPI mean increased by 0.29 (95% CI: 0.26–0.32); both were statistically significant. Also, by comparing the mean of TcPO2 in both groups, in the medical treatment group, TcPO2 mean was increased by 15.77 (95% CI: 13.16–18.37), while in the angioplasty group, the TcPO2 mean increased by 43.92 (95% CI: 40.59–47.25), and again both group means were statistically significant. No significant harm has been observed in any of the treatment groups.

A Kaplan–Meier log-rank test was used to elicit the statistical significance between the angioplasty-treated group and those who were treated conservatively with medication (i.e. cilostazol). The survival distributions for both groups were statistically significantly different, $\chi^2(1) = 9.687$, $p < 0.002$ (Figure 4).

Discussion

To date, there is no standard definitive treatment available for Buerger's disease, other than cigarette smoking cessation, which has proved to be most effective in the reduction of disease progression. Also, surgical revascularization using distal bypass is a good option for treatment if there

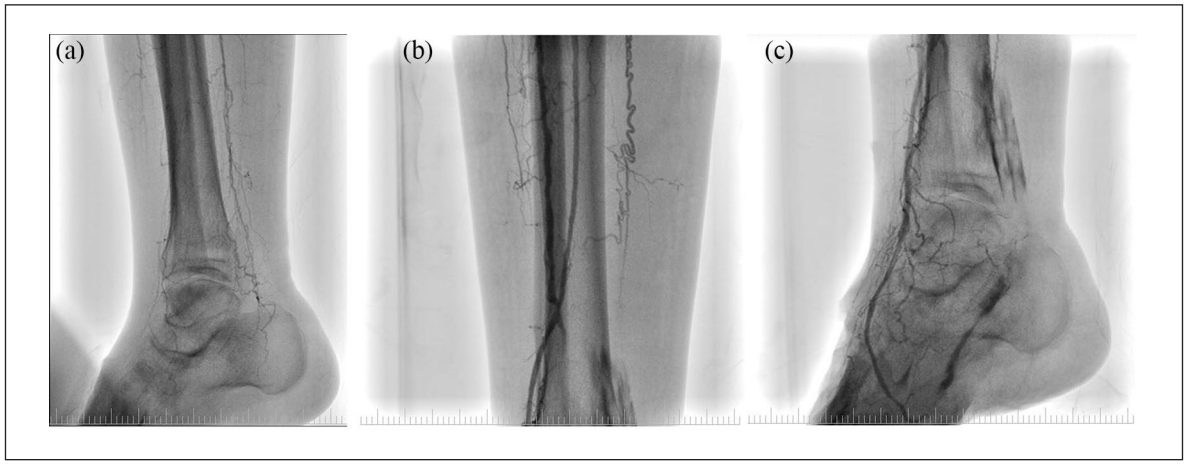

Figure 3. (a) No vessel run-off connected to the arch vessel before PTA, (b) lower leg angioplasty showing successful recanalization of the peroneal and ATA and (c) foot angiography showing the continuation of the ATA into the arch of the foot.

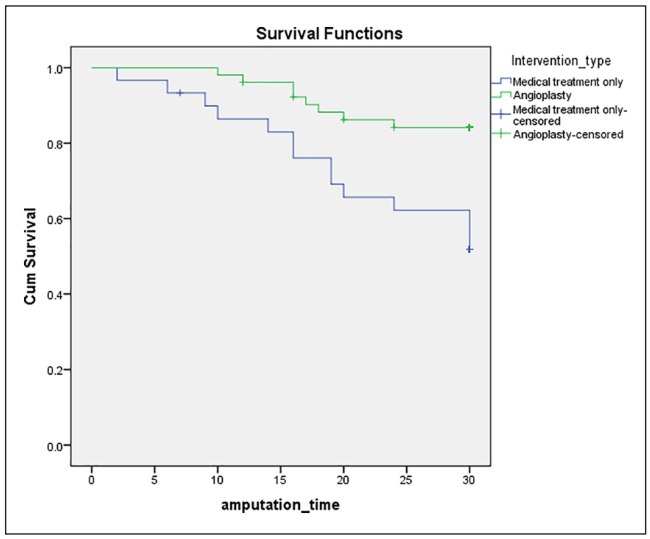

Figure 4. Kaplan–Meier survival curve for the amputation survival comparing both medical and angioplasty groups.

is a distal outflow. However, the feasibility to perform a bypass in those patients is limited because of the inflammatory nature of the disease and the luminal thrombotic lesions making it both technically difficult with a high incidence of failure. However, several studies reported that 7.4%–17.4% of patients with TAO required bypass surgery.[28] The patency rates of bypass graft were lower because primary and secondary patency rates were 48.8% and 62.5 % at 5 years, and 43.0% and 56.3 % at 10 years, respectively.[29] All bypass grafts, whether natural or synthetic, failed at 10 months following the intervention, and this was mostly attributed to the disease progression distal and proximal to the site of anastomosis.[6] Despite improvements in graft surveillance and new advances in vascular surgery, graft occlusion in the treatment of Buerger's disease persists. Endovascular revascularization for treatment of native vessel occlusion could be used as a treatment option after a failed bypass.[30,31]

Although thromboangiitis obliterans (TAO) mainly affects the infrapopliteal arteries, femoral and iliac arteries can also be affected.[6] Disease progression can be prevented by smoking cessation, prostaglandin analogues, sympathectomy and vascular endothelial growth factors injection.[32]

The pathological characteristics of Buerger's disease were recognized as preserved internal medial layer, concentric vasoconstriction and less calcification.[33] Radiological findings include the absence of arterial calcifications and development of robust collaterals referred to as "corkscrew collaterals" due to their appearance.[26,27] Notably, some authors suggest that the presence of these corkscrew vessels does not necessarily represent mature developed collaterals but rather might be a recanalized thrombosed native artery. Regardless, the appearance of corkscrew collaterals is often considered pathognomonic for TAO.[34] In this study, our observations confirmed those of Fujii et al.[26] regarding the clinical relevance of the severity of ischemia and the type of corkscrew collaterals and emphasized that patients with types III and IV usually will have a more severe clinical picture. We did not find any difference in the crossability of lesions whatever the severity of collaterals in contrary to Yuan et al.,[35] who reported difficult crossability of a proximal lesion surrounded by type III and IV collaterals using a soft guidewire; however, lesions surrounded by type I and II collaterals could be crossed easily.

All treated arteries were revascularized by ballooning only without stenting as there was no flow-limiting dissection, recoil or residual stenosis. This was different from the report done by Graziani et al.,[15] who used stenting primarily in 5 out of 20 patients to achieve satisfactory clinical and radiological success. Furthermore, some have argued that stenting should be avoided in patients with TAO, as the pathological inflammatory process and thrombosis associated with TAO may increase the incidence of in-stent stenosis.[36]

Furthermore, the advent of drug-eluting balloon (DEB) for the treatment of long femoropopliteal artery occlusion[37] may result in superior results in patients with TAO as well.[38]

In this study, we intended to achieve linear flow to the arch even in arteries without recognizable distal run-off on pre-operative imaging. Although several studies[6,39,40] only recommended the recanalization of arteries that have good distal run-off vessels to achieve good clinical outcomes and improve patency rates, this was also recommended in patients with TAO having infrapopliteal disease. Graziani et al.[15] treated infrapopliteal arteries and foot arteries extensively even without distal run-off in 17 out of the 19 cases, which consequently lead to improved clinical outcome in 16 out of 19 limbs with 100% limb salvage.

During the follow-up period, duplex studies revealed restenosis of 44% of supragenicular lesions and 18% of the infrapopliteal lesions which is different from that observed in arteriosclerosis as the reported incidence of below-the-knee restenosis reaches up to 65%.[41]

As smoking cessation was the only proposed choice for treating TAO together with medical treatment. We considered this as a critical point of the treatment. We ensured that smoking cessation would be implemented in both treatment groups, and due to the nature of the disease and the hypothesis behind its pathogenesis that relates to smoking, we considered resuming smoking would significantly increase the incidence of recurrence. Even though some authors did not find any statistically significant difference in those treated with angioplasty who maintained cessation and who resumed,[15] we can argue that these results are not strong enough to detect that difference because these studies were small and underpowered to discover such difference. For that, to reach a point where we can identify whether smoking can make a difference, a large randomized trial should be conducted. A study showed that if one continues to smoke, this can significantly affect the durability of the proposed intervention and the efficacy is dependent on the duration of abstinence from smoking.[42]

The lower incidence of infragenicular restenosis in this study could be explained by the aggressive ballooning for higher than average pressures and longer duration. Hypothetically, this might result in periarterial sympathectomy and thus minimization of vasoconstriction, recoil and stenosis, all translating into improved long-term patency and durable ulcer healing. The role of periarterial sympathectomy has been documented in the study of Hartzell et al.[43] who reported clinical improvement with total healing of ulcers in patients suffering from autoimmune disease; however, this was not evident in those with ulcers due to atherosclerotic disease. However, a study published by Tang et al.[44] showed the uncertain significance of the use of radiofrequency ablation for treating TAO; the authors were unsure of the effect because of the small sample size. A commentary to the paper published by Hafezi and Modaghegh[45] discussed the results of Tang et al. study and suggested that the short-term effect produced by sympathectomy is not sufficient alone to maintain the clinical benefit obtained in some patients.

Finally, the limitation of our study was that all patients were recruited from one center, and the technique was done by different surgeons and a small number of cases.

Conclusion

Aggressive endovascular balloon angioplasty can be an essential option in the treatment of patients with Buerger's disease and may result in excellent long-term patency with a statistically significant difference to only conservative measures regarding ulcer healing, pain or major amputation, possibly as a result of denervation of the periarterial sympathetic plexus.

Authors' note

Part of this work was presented at the Multidisciplinary European Endovascular Therapy (MEET) Rome, 2011.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from *Mansoura University Institutional Review Board (R.18.05.187). Consent was verbally taken and documented on the patient file with the patient signature during the clinic appointment and again was reviewed with the patient immediately before the start of the procedure, detailed explanation of the disease, the proposed treatment, process of randomization and the possible complications were explained to the patients and this process was approved by the Institutional Review Board in our university.

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Informed consent

Consent was verbally taken and documented on the patient file with the patient signature during the clinic visit appointment and again was reviewed with the patient immediately before the start of the procedure.

Trial registration

This trial was not registered, but IRB approval was locally obtained in our university.

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