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Effect of Surgical Sympathectomy in Patients Diagnosed with Thromboangiitis Obliterans Compared to Pharmacotherapy and Bypass Surgery

Javad Salimi[1], Maryam Abbasi[2], Fatemeh Chinisaz [3] and Seyed Amir Miratashi Yazdi[4*]

[1]Professor of Surgery, Vascular & Endovascular Surgeon, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of General Surgery, Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Students` Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Surgery, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

*** *Corresponding author:*** Seyed Amir Miratashi Yazdi, Department of Surgery, School of Medicine, Tehran University of medical sciences, Tehran, Iran. Email: mehmetakifnas@gmail.com

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Abstract

Background: Thromboangiitis obliterans (TAO) is a vasculopathy involving small and intermediate vessels of extremities with various medical and surgical treatment strategies.
Objectives: This cohort study aimed to compare the outcomes of medical and surgical interventions in patients with TAO.
Methods: Patients with a definite diagnosis of TAO were enrolled in the study and evaluated on the first day, as well as three and six months follow-up visits. A total of 70 patients with TAO were followed for 30 months. Improvements in the primary complaints (claudication of calves and soles, rest pain, paresthesia, thrombophlebitis migrans, gangrene, scars, Raynaud's phenomenon) were compared between the groups.
Results: In terms of gender, 98.6% of participants were male. The mean age of the patients was 43.24 ±9.8 years. Based on the results, 37 sympathectomy surgery, 11 amputation surgery, 15 bypass surgery, and 12 medical therapies with ILOPROST were considered for the patients (Medical treatment as combination therapy in patients with severe symptoms). The final results demonstrated that primary complaints were significantly improved in patients who underwent bypass surgery than in others.
Conclusion: As evidenced by the obtained results, patients in our study significantly benefited more from bypass surgery than sympathectomy and pharmacotherapy.

Keywords: Bypass surgery, Buerger's disease, Iloprost, Surgical sympathectomy, Thromboangiitis obliterans (TAO)

1. Background

Burger disease or Thromboangiitis obliterans (TAO) is a type of vasculitis leading to cell-rich thrombus and vessel occlusion mostly affecting small and medium-sized arteries and veins in upper and lower limbs in young smoker men. Thrombus formation in TAO follows a diffuse segmental pattern, and despite the inflammatory nature of the disease, the vascular wall structure and elastic lamina remain intact. The etiology of the disease is still unknown, and tobacco consumption in any form is the major risk factor for the disease. Coagulopathies, immune deficiencies, and dysfunction of the endothelial layer may play a key role in the initiation of TAO in some patients. This disease manifests as vascular insufficiencies, such as intermittent claudication, rest pain, Raynaud phenomenon, ischemic ulcers, and superficial thrombophlebitis (1).

The TAO is a multifactorial disease affected by both genetic background and environmental factors. Various studies have pointed to the association between TAO and different HLA alleles. The high frequency of the DRB1*04 DRB1*16:01, A*03:01, and A*29:01, as well as the low frequency of the DRB1*01:01 alleles, have been reported in the Iranian population with TAO (2). Since there are no specific angiographic findings, laboratory tests, or positive serologic markers to diagnose TAO, diagnosis is made based on the patient's symptoms and clinical data. Although many diagnostic criteria have been proposed over the years, no complete and specific diagnostic criteria exist for the TAO. The traditional criteria of Shionoya are the most used diagnostic criteria, including a history of tobacco or cigarette consumption, infra popliteal vascular involvements or upper limb involvements or migrans phlebitis, the onset of the symptoms before the age of 50, and the absence of risk factors for atherosclerotic disease (3, 4).

Other diagnostic interventions, such as angiography, may help confirm the disease (5). A study by Ramin et al. proposed diagnostic criteria with 95.1% sensitivity and 78.7% specificity, demonstrating better efficacy, especially in the Iranian population, compared to Papa's diagnostic criteria (6). The therapeutic approaches for TAO are pharmacological, surgical, or both. Pharmacological treatment is usually used to improve the blood flow (perfusion) in the extremity. The most common pharmacological treatments used are aspirin, cilostazol, prostanoids, and bosentan (7-9)
Surgical sympathectomy amputation and arterial plastic surgery are the most commonly performed

surgical treatments (10). Since there is no comprehensive and complete guideline for the treatment of TAO, it is not yet known which treatment is the best for reducing the symptoms of the disease. In light of the aforementioned issues, the present study aimed to compare surgical sympathectomy outcomes with bypass surgery and conventional pharmacotherapy.

2. Objectives

This cohort study aimed to compare the outcomes of medical and surgical interventions in patients with TAO.

3. Methods

3.1. Study designs and patients

In this prospective cohort study, 70 patients with TAO were considered for evaluation between 2016-2019. The protocol of the study was approved by the review board of the Tehran University of Medical Sciences, and it was according to Helsinki's ethical code and its later amendments. Patients gave written informed consent before any participation in the study. The inclusion criteria were as follows: all patients diagnosed with TAO according to the criteria of Shionoya admitted to Sina Hospital for therapeutic interventions within 30 months. Criteria of Shionoya are the most used diagnostic criteria, including a history of tobacco or cigarette consumption, infra popliteal vascular involvements or upper limb involvements or migrans phlebitis, the onset of the symptoms before the age of 50, and the absence of risk factors for atherosclerotic disease (3, 4).

On the other hand, the exclusion criteria entailed an age range of 25-75, surgical unfitness, a history of diabetes mellitus, and unwillingness to participate in the study. Demographic parameters, including gender, age, occupation, and smoking, were taken by a designed questionnaire. Moreover, a history of previous interventions was recorded, including echocardiography, angiography, hemostasis tests, drug therapy, and surgical therapy. The patients were evaluated one day, as well as three and six months, after sympathectomy surgery, bypass surgery, and pharmacotherapy.

3.2. Missing Data

Six patients were out of reach for the follow-ups and were excluded. One patient did not accept any therapeutic intervention, and one expired three months after the surgery; these two cases were excluded from the study (Figure 1).

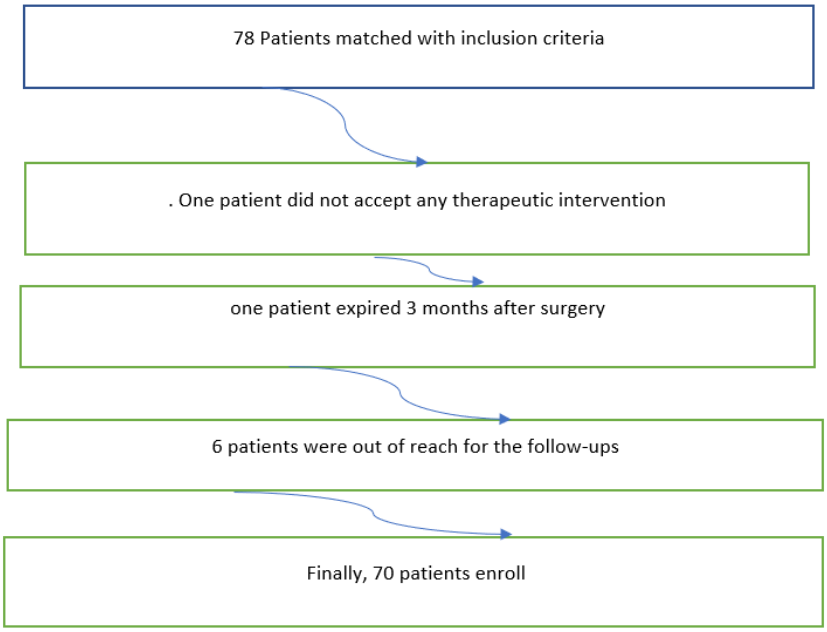

Figure 1. Patients enrolling

3.3. Outcome measures

Data associated with symptoms of the disease, including claudication of calves and soles, rest pain, paresthesia, thrombophlebitis migrans, gangrene, scars, and Raynaud's phenomenon, as well as the duration of the symptoms, were collected through a well-validated questionnaire before the interventions, one day, three months, and six months after the interventions and the improvements of patients' symptoms were compared. The data were collected via phone calls in post-operative three and six-month follow-ups.

3.4. Statistical analysis

The data were analyzed in SPSS software (version 23.5). Data were expressed either as mean ± standard deviation (SD) or by percentages. Univariate associations were assessed by Pearson

Chi-square. A p-value of less than 0.05 was considered statistically significant.

4. Results

A total of 70 patients were followed up. In terms of gender, the majority of subjects (98.6%) were male.The mean age of the patients was 43.24 ±9.8 years. Patients' demographic data are displayed in Table 1. The limb involvements in patients were as follows: cases of Left lower extremity (n=44; 62.9%), right lower extremity (n=45; 63.3%), left upper extremity (n=13; 18.6 %), and right upper extremity (n=16; 22.9%). The symptoms of TAO that patients presented with were as follows: claudication of calf and sole were reported in 44 (62.9%) and 40 (57.1%) cases, respectively. Rest pain, paresthesia, thrombophlebitis migrans, gangrene, ulcers, and Raynaud phenomenon were observed in 71.4%, 65.7%, 8.6%, 71.4%, 80%, and 24.3% of patients, respectively.

Table 1. Prevalence of signs and symptoms of the patients before the intervention

Variable	Percentage n (%).
Male-female ratio	70.42%
Calf claudication	62.9%
Plantar Claudication	57.1%
Rest pain	71.4%
paresthesia	65.7%
thrombo-phlebitis migrans	8.6%
Gangrene	71.4%
Ulcer	80 %
Raynaud	24.3%

Therapeutic interventions were as follows: sympathectomy surgery (n=37;52.9%), lumbar sympathectomy surgery (28), thoracic sympathectomy surgery(9), amputation surgery(n=11; 15.7%), bypass surgery (n=15; 21.4%), (femoro-peroneal bypass (n=1; 1.4%), left femoropopliteal bypass (n=2; 2.9%), a right femoropopliteal bypass (n=4 5.7%), and anterior femorotibial bypass (n=1; 1.4%), aorto-femoral bypass (n=4; 5.7%), ilio-femoropopliteal bypass (n=1), left iliofemoral bypass (n=1), and ilio-popliteal with sympathectomy (n=1). Moreover, 12 (17.1%) patients received the ILOPROST drug. Post-operative outcomes of the patients who underwent sympathectomy surgery, bypass surgery, and pharmacotherapy are presented in (Table 2-6).

Table 2. Post-operative improvements of symptoms in patients who underwent sympathectomy, bypass surgery, and pharmacotherapy

		claudication of calf n (%).	Plantar claudication n (%)	Paresthesia n (%). a	Migrans phlebitis n (%)	Gangrene n (%).	Ulcer n (%).	Rest pain n (%).	Reynaud n (%).
Sympathectomy Post-op improvements	1 Day Post-operatio	13 (61.9%)	15 (52.6%)	19 (65.5%)				18(64.3%)	4 (50%)
	3 Month Follow Up	14 (60.9%)	11 (50%)	15 (53.6%)	4 (80%)	10 (55.6%)	15 (57.7%)	15 (51.7%)	4 (50%)
	6 Month Follow Up	14 (53.8%)	10 (43.5%)	15 (53.6%)	5 (83.3%)	11 (55%)	16 (61.5%)	19 (61.3%)	5 (62.5%)
Bypass surgery post-op improvements	1 Day Post-operation	8 (66.7%)	8 (72.7%)	8 (61.5%)				9 (75%)	1 (25%)
	3 Month Follow Up	8 (66.7%)	8 (72.7%)	9 (64.3%)		5 (62.5%)	8 (66.7%)	10 Cases (83.3%)	(76.9%)
	6 Month Follow Up	9 (75%)	9 (81.8%)	10 (83.3%)	2 (66.7%)	7 (87.5%)	10 Cases (83.3%)	11 Cases (91.7%)	3 (75%)
Pharmacotherapy improvements	1 Day Post-operation	1 (100%)	2(100%)	2(100%)		1 (50%)	1 (20%)	1 (25%)	1 (100%)
	3 Month Follow Up	1 (100%)	2(100%)	2(100%)		2 (100%)	2 (33.3%)	1 (25%)	
	6 Month Follow Up	1 (100%)	1 (50%)	3 (75%)		2 (66.7%)	2 (33.3%)	3 (60%)	

Table 3. Post-operative symptoms in subjects who quitted smoking and continue smoking after sympathectomy

	symptoms	Claudication of calf n (%).	Plantar claudication n (%).	Paresthesia n (%).	Migrans phlebitis n (%).	Gangrene n (%).	Ulcer n (%).	Rest pain n (%).	Raynaud phenomenon n (%).
1 day Post op	Stop Smoking/ No Improvements	3 (42.9%)	3 (50%)	5 (45.5%)	1 (33.3%)	3 (50%)	5 (50%)	4 (36.4%)	3 (60%)
	Stop Smoking / Improvements	4 (57.1%)	3 (50%)	6 (54.5%)	2 (66.7%)	3 (50%)	5 (50%)	7 (63.6%)	2 (40%)
	Continue Smoking / No Improvements	4 (40%)	5 (45.5%)	4 (28.6%)	0 (0%)	1 (33.3%)	3 (42.9%)	3 (27.3%)	1 (33.3%)
	Continue Smoking / Improvements	6 (60%)	6 (54.5%)	10 (71.4%)	2 (100%)	2 (66.7%)	4 (57.1%)	8 (72.7%)	2 (66.7%)
3 Month Follow Up	Stop Smoking/ No Improvements	2 (28.6%)	3 (42.9%)	5 (45.5%)	1 (33.3%)	3 (33.3%)	4 (36.4%)	5 (41.7%)	2 (40%)
	Stop Smoking / Improvements	5 (71.4%)	4 (57.1%)	6 (54.5%)	2 (66.7%)	6 (66.7%)	7 (63.6%)	7 (57.3%)	3 (60%)
	Continue Smoking / No Improvements	6 (50%)	7 (53.8%)	7 (53.8%)	0 (0%)	3 (42.9%)	6 (54.5%)	6 (54.5%)	1 (50%)
	Continue Smoking / Improvements	6 (50%)	6 (46.2%)	6 (46.2%)	2 (100%)	4 (57.1%)	5 (45.5%)	5 (45.5%)	1 (50%)
6 Month Follow Up	Stop Smoking/ No Improvements	4 (50%)	4 (57.1%)	4 (36.4%)	1 (33.3%)	2 (20%)	3 (27.2%)	3 (23.1%)	1 (25%)
	Stop Smoking / Improvements	4 (50%)	3 (42.9%)	7(63.6%)	2(63.7%)	8 (80%)	8 (72.8%)	10 (76.9%)	3 (75%)
	Continue Smoking / No Improvements	7(50%)	8(57.1%)	8(61.5%)	(0%)	5(62.5%)	6 (54.5%)	6(50%)	2 (50%)
	Continue Smoking / Improvements	7(50%)	6(42.9%)	5(38.5%)	3(100%)	3 (37.5%)	5(45.5%)	6 (50%)	2 (50%)

Table 4. Comparison between post-sympathectomy recovery rate and post-bypass recovery rate

Symptoms	P-value (1 day after surgery)	P-value (3-month F/Us)	P-value (6-month F/Us)
Claudication of calf	0.005	0.005	0.003
Ulcer	0.028	0.001	0.005
Rest pain	0.001	0.005	0.001
Plantar claudication	0.001	0.001	0.007

*Chi square test

Table 5. Comparison between post-sympathectomy recovery rate and post-pharmacotherapy recovery rate

Symptoms	P-value(1 day after surgery)	P-value(3- Month Follow Up)	P-value(6- Month Follow Up)
Claudication of calf	0.125	0.112	0.127
Ulcer	0.064	0.157	0.087
Rest pain	0.098	0.157	0.03
Plantar claudication	0.089	0.075	0.176

* Chi square test

5. Discussion

This study aimed to compare sympathectomy surgery outcomes in patients with TAO with bypass surgery and drug therapy outcomes. Patients in our study significantly benefited more from bypass surgery than sympathectomy and pharmacotherapy. There are various therapeutic options for TAO which are pharmacotherapy with diverse medications (prostacyclin analog (iloprost, and clinprost, aspirin, prostaglandin analog, folic acid cilostazol, clopidogrel, and pentoxifylline) (11). Pharmacotherapy with different medications may help patients reduce ischemic ulcers and rest pain; nonetheless, it has no effects on preventing the disease progression.

Quitting the consumption of cigarettes and tobacco in any form is the only fundamental treatment for Buerger's disease, and all the other surgical and medical treatments are palliatives. Therefore, the results of the studies strongly prove

Table 6. Post-operative symptoms in cases who quitted smoking and continue smoking after bypass surgery

	symptoms	Claudication of calf n (%).	Plantar claudication n (%).	Paresthesia n (%).	Migrans phlebitis n (%).	Gangrene n (%).	Ulcer n (%).	Rest pain n (%).	Raynaud phenomenon n (%).
1 day Post op	Stop Smoking/ No Improvements	3 (37.5%)	2 (28.6%)	3 (42.9%)	1 (100%)	2 (25%)	2 (40%)	2 (28.6%)	2 (100%)
	Stop Smoking / Improvements	5 (62.5%)	5 (71.4%)	4 (57.1%)	2 (66.7%)	3 (75%)	3 (60%)	5 (71.4%)	(0%)
	Continue Smoking / No Improvements	(0%)	(0%)	(0%)	(0%)	(0%)	1 (100%)	(0%)	(0%)
	Continue Smoking / Improvements	2 (100%)	2 (100%)	3 (100%)	2 (100%)	(0%)	0 (0%)	3 (100%)	1 (100%)
3 Month Follow Up	Stop Smoking/ No Improvements	3 (37.5%)	2 (28.6%)	2 (25%)	1 (100%)	1 (16.7%)	2 (25%)	1 (12.5%)	2 (100%)
	Stop Smoking / Improvements	5 (62.5%)	5 (71.4%)	6 (75%)	(0%)	5 (83.3%)	6 (75%)	7 (87.5%)	0 (0%)
	Continue Smoking / No Improvements	(0%)	(0%)	1 (33.3%)	(0%)	(0%)	1 (50%)	(0%)	0 (0%)
	Continue Smoking / Improvements	2 (100%)	2 (100%)	2 (66.7%)	(0%)	(0%)	1 (50%)	2 (100%)	0 (0%)
6 Month Follow Up	Stop Smoking/ No Improvements	3 (37.5%)	2 (28.6%)	2 (25%)	1 (50%)	2 (20%)	2 (22.2%)	1 (12.5%)	1 (33.3%)
	Stop Smoking / Improvements	5 (62.5%)	5 (71.4%)	6 (75%)	1 (50%)	8(80%)	7 (77.8%)	7 (78.5%)	2 (66.7%)
	Continue Smoking / No Improvements	(0%)	(0%)	(0%)	(0%)	(0%)	(0%)	(0%)	(0%)
	Continue Smoking / Improvements	2(100%)	2 (100%)	3 (100%)	1 (100%)	1(100%)	2 (100%)	3 (100%)	1 (100%)

the correlation between tobacco use and exacerbation of the disease, leading to non-healing ulcers and limb amputation (1, 12). Nonetheless, it seems that discontinuing smoking on its own is not sufficient for the treatment of patients with critical limb ischemia, and other therapeutic interventions are needed as well (13). Surgical sympathectomy reduces the spasms of arteries in patients with TAO; nonetheless, it is still unclear how the surgery improves the symptoms. It seems that surgical sympathectomy is helpful in patients with persistent pain and non-healing ischemic lesions that have abstained from the consumption of tobacco (14).

The efficacy of sympathectomy in short-term follow-ups was evaluated in a study by N. Nakajima, and the results were as follows: 60% of all patients illustrated marked improvements in symptoms. 25% of them improved in symptoms, and only 1.5 % had aggravation in symptoms. The study also confirmed that advanced symptoms, such as rest pain and ulcers, were also improved after sympathectomy. Remission in symptoms in long-term follow-ups was recorded in 83% of patients, the effectiveness of the surgery lasted in 50% of them after five years, and just 10% of the patients had no change in symptoms (15).

Although surgical sympathectomy improves severe symptoms in patients, complete remission only occurs if they stop smoking. Stop smoking can heal ischemic lesions and reduce the risk of amputation (12). The correlation between the recovery rate in people who quit smoking and continue smoking after a sympathectomy is detailed in Table 3. Among 70 patients, 15 cases underwent bypass surgery. In 6-month follow-ups, no treatment failure was reported. Moreover, improvements in symptoms in one-day, 3-month, and 6-month follow-ups were significant. Improvements and remission of the symptoms were around 70%-80%. The results were much better than the outcomes in patients who underwent sympathectomy surgery and pharmacotherapy.

A study by Dilege et al. on 27 patients who underwent bypass surgery confirmed successful bypasses with a 92.5% salvage rate in follow-ups in three years. Moreover, 31 patients underwent bypass surgery in a study by Ohta, and the post-op results displayed an 85.4% salvage rate in 10-year follow-ups. Nonetheless, bypass surgery seems to be a beneficial surgical treatment with a high amputation-free survival rate. This procedure is difficult and unavailable due to a lack of possible, sufficient vessels, and diffuse segmental pattern of thrombus in

distal vessels. Surgical sympathectomy usually is performed when bypass surgery is impossible (16).

According to the results of the comparison between sympathectomy and bypass, it seems that patients benefited significantly more from bypass surgery than sympathectomy. Nonetheless, there were no meaningful results of comparison between sympathectomy and pharmacotherapy. However, a randomized controlled study that compared sympathectomy with ILOPROST demonstrated that ILOPROST is more effective in healing ulcers and rest pain in patients with TAO (17).

Although several articles, including our study, confirmed that patients benefit from bypass surgery in short-term follow-ups, according to recent studies, long-term outcomes are not satisfactory (1). One main reason underlying the unsatisfactory long-term outcomes of bypass surgery is that patients start smoking after a while which reactivates TAO. In a study performed by Ohta et al., 31 patients underwent bypass surgery. Primary graft patency was 41%, 32%, and 30% at 1, 5, and 10 years, respectively. Secondary graft patency was 54%, 47%, and 39% at 1, 5, and 10 years of follow-up, respectively (18).

Unfortunately, very limited studies have evaluated treatment approaches for Buerger's disease, and due to the lack of any accurate protocol for the treatment of TAO and the low prevalence of the disease, it is not possible to make a definite and comprehensive conclusion about the most effective therapeutic interventions. The main limitation of our study is the lack of long-term follow-up. Future studies should be designed to compare sympathectomy, bypass, and medical therapy for a long time.

6. Conclusion

The only very effective and fundamental treatment of TAO is tobacco and cigarette cessation. Patients in our study significantly benefited more from bypass surgery than sympathectomy and pharmacotherapy. Surgical sympathectomy and bypass surgery are the most common surgical treatments for TAO.

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Footnotes

Conflicts of Interest: The authors have no relevant financial or non-financial interests to disclose

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