Türk Göğüs Kalp Damar Cerrahisi Dergisi 2013;21(2):346-352
doi: 10.5606/tgkdc.dergisi.2013.7409

Original Article / Özgün Makale

Effectiveness of the cascade filtration technique in the management of inoperable leg ischemia

İnoperabl bacak iskemisinin tedavisinde kaskad filtrasyon tekniğinin etkinliği

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Background: This study aims to investigate the effectiveness of the cascade filtration technique in individuals with peripheral vascular disease who are candidates for amputation.

Methods: Twelve patients (9 males, 3 females; mean age 62.4±7.2 years; range 45 to 75 years) were included in the study. For the evaluation of the efficacy of this procedure, measurements of serum albumin, fibrinogen, immunoglobulin M, alpha-2 macroglobulin, low density lipoprotein (LDL) cholesterol, fibronectin, von Willebrand factor levels, blood viscosity, and transcutaneous oxygen saturation ($tcPO_2$) were obtained before and after the procedure at sessions 1, 4, and 7.

Results: A statistically insignificant increase in $tcPO_2$ values and a significant decrease in viscosity were determined (p=0.019). Fibronectin, von Willebrand factor, and viscosity levels were significantly decreased at the end of protocol, compared to baseline values. Various degrees of improvement were noted in seven of the 10 patients. After the completion of the protocol, amputation from a more distal level than previously planned was performed in three patients.

Conclusion: Cascade filtration, despite its high cost, appears to be an effective treatment alternative which limits or prevents amputation.

Key words: Cascade filtration; hemorheotherapy; ischemic leg; peripheral artery disease; rheopheresis.

Amaç: Bu çalışmada amputasyona aday periferik vasküler hastalığı olan kişilerde kaskad filtrasyon tekniğinin etkinliği araştırıldı.

Çalışma planı: Çalışmaya 12 hasta (9 erkek, 3 kadın; ort yaş 62.4±7.2 yıl; dağılım 45-75 yıl) dahil edildi. Bu işlemin etkinliğini değerlendirmek için 1, 4. ve 7. seanslardan önce ve sonra serum albümin, fibrinojen, immünoglobulin M, alfa-2 makroglobulin, düşük yoğunluklu lipoprotein (LDL) kolesterol, fibronektin, von Willebrand faktör düzeyleri, kan viskozitesi ve transkütanöz oksijen satürasyonu ($tcPO_2$) ölçüldü.

Bulgular: İstatistiksel olarak $tcPO_2$ değerlerinde anlamlı olmayan bir artış ve viskozitede anlamlı bir azalma belirlendi (p=0.019). Başlangıç değerlerine kıyasla protokol sonunda fibronektin, von Willebrand faktör ve viskozite seviyeleri anlamlı derecede azaldı. On hastanın yedisinde çeşitli derecelerde iyileşme kaydedildi. Protokol tamamlandıktan sonra, üç hastada amputasyon başlangıçta planlanandan çok daha distal seviyeden yapıldı.

Sonuç: Kaskad filtrasyonu, yüksek maliyetine rağmen, amputasyonu önleyen veya sınırlayan etkili bir tedavi seçeneği gibi görünmektedir.

Anahtar sözcükler: Kaskad filtrasyonu; hemoreoterapi; iskemik bacak; periferik arter hastalığı; reoferez.

Peripheral vascular diseases, most often caused by atherosclerosis, negatively affect the arterial circulation of the legs. Diabetes, cardiovascular and cerebrovascular diseases, and peripheral arterial occlusive diseases (e.g., Burger's disease, vasculitis, and arterial trauma) also lead to impairment of leg microcirculation.[1,2] In addition to inflammatory and degenerative diseases that affect the vascular system, alterations in plasma protein

Available online at
www.tgkdc.dergisi.org
doi: 10.5606/tgkdc.dergisi.2013.7409
QR (Quick Response) Code

Received: July 18, 2012 *Accepted:* October 16, 2012

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composition and an increase in the number of blood cells can also lead to impairment of microcirculation by causing hyperviscosity.[3] The most significant risk factors for the development of peripheral vascular disease are advanced age (>55 years), smoking, hyperlipidemia, diabetes mellitus (DM), hyperviscosity, hypertension, and high plasma levels of fibrinogen and homocysteine.[1,4,5]

Limitation of blood flow while the patient is walking causes functional limb ischemia and muscle pain, which is also known as intermittent claudication. As the disease progresses, ischemic pain may also be present during rest. This process leads to ulcers and gangrene. If this state, commonly called critical ischemic limb, is not treated promptly, amputation may be inevitable in 19.6% of such patients.[1,2]

Treatment of microcirculation disorders is often symptomatic (e.g., laser photocoagulation, endovascular treatment, and bypass grafting). Isovolemic or hypervolemic hemodilution and hyperbaric oxygenation therapy have had limited success. Therefore, amputation is often required in patients with peripheral vascular disease that is not suitable for reconstruction and those with fixed flexion deformities or extensive tissue loss.[2,3]

Hemorheology focuses on an improvement of blood flow characteristics in the microcirculation through a reduction in blood viscosity.[4] The rheological characteristics of the blood are determined by blood and plasma viscosity, erythrocyte deformability, and erythrocyte aggregation. Measurements of these parameters provide information about the rheological properties of the blood.[6]

Plasma protein composition is directly related to blood and plasma viscosity and erythrocyte aggregation.[3] The contribution of plasma proteins to viscosity varies according to their molecular weight and shape. Small globular molecules, such as albumin, have little effect on plasma viscosity, but high molecular weight proteins, such as fibrinogen, have strong effects. Proteins increase blood viscosity not only by increasing plasma viscosity, but also by accelerating erythrocyte aggregation.[6]

Cascade filtration, a type of membrane differential filtration, is one of the extracorporeal plasma treatment models used in hemorheotherapy. High molecular weight proteins in human plasma, for example fibrinogen, alpha-2-macroglobulin, low-density lipoprotein (LDL) cholesterol, immunoglobulin M (IgM), fibronectin, and von Willebrand factor (vWF), are eliminated by this process. Thus, plasma and blood viscosity as well as erythrocyte aggregation are reduced, and the microcirculation is improved.[3,7]

Transcutaneous oxygen saturation can be used as a diagnostic method to indicate claudication and determine the functional capacity of an extremity.[8,9] This direct and noninvasive method can be used to determine local cutaneous oxygenation in patients with peripheral vascular disease and was used in the current study to evaluate the effectiveness of the cascade filtration procedure in individuals with peripheral vascular disease who were beyond the limits of surgical intervention and who were candidates for amputation.

PATIENTS AND METHODS

Twelve patients (9 males, 3 females; mean age 62.4±7.2 years; range 45 to 75 years) were included in the study. However, because one patient withdrew and another patient was excluded due to sepsis, only 10 patients were able to complete it. The demographic and clinical features of the patients are summarized in Table 1.

The inclusion criteria for the current study were as follows: patients who were unresponsive to surgical revascularization or who required a second round of revascularization, but had inoperable lesions; patients

Table 1. Demographic and clinical features of the patients

Case	Gender	Age	DM	HT	Smoking	Previous treatment	Wagner stage	Extremity
1	M	76	+	+	+	Femoral-popliteal bypass	2	Bilateral
2	M	67	+	-	-	Medical	3	Right
3	F	47	+	+	+	Iliac artery endarterectomy, sympathectomy	3	Bilateral
4	M	75	+	+	+	Medical	4	Bilateral
5	M	71	-	+	-	Femoral-popliteal bypass	4	Bilateral
6	M	63	-	-	+	ABF, femoral-popliteal bypass	2	Right
7	M	65	-	+	+	ABF, femoral-popliteal bypass x 2	5	Bilateral
8	M	51	-	-	+	Sympathectomy	3	Bilateral
9	M	64	+	-	-	Medical	4	Bilateral
10	F	45	-	-	+	Medical	3	Left

DM: Diabetes mellitus; HT: Hypertension; ABF: Aortobifemoral bypass.

Table 2. Transcutaneous oxygen saturation values before and after the cascade filtration procedure

	Transcutaneous oxygen saturation values (mmHg)					
	Session 1		Session 4		Session 7	
Case	Before	After	Before	After	Before	After
1	17	15	14	16	13	15
2	14	15	16	13	9	11
3	16	27	23	28	36	30
4	14	33	19	35	39	18
5	12	20	13	28	37	21
6	12	9	11	13	8	9
7	13	20	12	26	33	19
8	19	22	17	18	15	17
9	20	35	23	38	44	30
10	16	27	23	37	48	30

with critical leg ischemia for whom maximum medical treatment was not effective and amputation was required; patients who had stenotic lesions distal to the popliteal artery on peripheral angiography which were considered to be inoperable for revascularization surgery by our clinical council; and patients with grade 2 and above lesions according to the Wagner scale. The study was approved by the hospital ethics board, and informed consent was obtained from all patients before inclusion. All procedures were performed in accordance with the Declaration of Helsinki.

An intravenous line was placed in both arms of all patients under sterile conditions using an Angiocath™ (Becton Dickinson, Sandy, UT, USA) or fistula needle in the apheresis unit to provide a minimum flow rate of 70 ml/min. In those cases where an appropriate peripheral vascular venous line could not be established, a central venous line was inserted using a double lumen hemodialysis catheter. The blood was withdrawn from one line at a mean flow rate of 70 ml/min. Following apheresis, macromolecules were separated into the waste bag, and the blood was readministered to the patient via the other line. The extracorporeal line was filled with isotonic fluid before the procedure to avoid excessive blood withdrawal and to prevent the risk of hypotension.

In order to assess the effectiveness of the procedure, the transcutaneous oxygen saturation and plasma viscosity were measured before and after the procedure at sessions one, four, and seven. Blood samples were also withdrawn before and after the procedure at the same sessions to monitor the changes in fibrinogen, alpha-2 macroglobulin, vWF, fibronectin, LDL-cholesterol, albumin, and IgM levels.

Plasma viscosity was measured using 0.7 ml of the initial and final plasma withdrawn into the waste bag using a viscosimeter. A transcutaneous oxygen saturation probe was placed within the ischemic leg

Table 3. Laboratory results of the cascade filtration procedure at baseline and at the end of session seven

Case	LDL-cholesterol (mg/dL)	vWF (IU/mL)	Fibronectin (mg/L)	Alpha-2 macroglobulin (mg/dL)	IgM (mg/dL)	Fibrinogen (mg/dL)	Albumin (g/dL)
1 B	101.2	0.98	413.32	3.78	117.3	529.42	3.9
1 A	23	<0.10	105.74	0.56	<14	186	1.5
2 B	93.6	0.78	384.54	1.28	183.2	800	2.7
2 A	49.2	<0.10	102.34	0.47	35.4	223.4	2.3
3 B	87	1.24	328.43	1.28	123.2	373.6	3.6
3 A	31	0.21	98.46	0.28	33.2	444.9	3.1
4 B	54.6	1.56	303.25	1.56	32	697.2	3.6
4 A	54.8	0.32	83.75	1.08	<14.0	136.1	3.4
5 B	127.8	1.67	456.45	1.33	48.3	891.3	3.4
5 A	36	0.38	148.72	0.55	<14.0	118.1	2.1
6 B	108	0.85	356.43	3.86	116.1	925	3.1
6 A	3	<0.10	98.23	0.49	<14.0	296.4	2.1
7 B	163.2	0.92	313.56	2.13	93.2	437.92	4.1
7 A	55.0	<0.10	94.37	0.81	34.2	136.1	3.0
8 B	105	1.65	467.43	1.64	166.5	891.3	3.3
8 A	29.0	0.35	157.48	0.43	43.5	123.6	2.0
9 B	83.8	1.38	384.76	1.82	186	453.2	3.9
9 A	4.2	<0.10	103.44	0.51	28	81.4	2.9
10 B	80.4	0.87	279.64	1.79	98.2	392.9	3.4
10 A	82	<0.10	68.35	0.65	26.7	444.9	3.1

LDL: Low density lipoprotein; vWF: von Willebrand factor; IgM: Immunoglobulin M.

regions supplied by the tibialis posterior or anterior arteries, and this was monitored and recorded every 20 minutes throughout the apheresis procedure, starting from the beginning. Anticoagulant citrate dextrose solution A (ACD-A) was used to prevent clotting and to maintain continuous flow within the lines. Dilutions from 1/8 to 1/24 could be used by the device, but we generally preferred 1/12. A calcium infusion was initiated, without waiting for the session to end, whenever clinical findings of hypocalcemia (e.g., numbness and tingling sensations in the hands, tetanic contractions, and muscle twitches) were noted in the patients. The plasma volume of the patients was determined from their weight, and a plasma amount of approximately 1.5 times the plasma volume was processed in each patient. This corresponded to approximately 4000-4500 mL of plasma volume. The duration of the procedure ranged from two to five hours, depending on the flow rate. When the procedure was delayed for various reasons, the patient was allowed to eat. The first two sessions were performed within the same week, and the remaining five sessions were performed every two weeks. Thus, a total of seven sessions of cascade filtration were completed in 11 weeks.

Data analysis was performed using Epi Info™, version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA), and statistical differences were evaluated by a chi-square test and Pearson's correlation test.

The primary endpoint of the study was limb salvage without major amputation at 11 weeks. The secondary endpoint of death, peripheral vascular endpoint, defined as a major amputation or progressive limb ischemia, and other secondary endpoints such as wound healing, quality of life, and severe adverse effects, such as septic symptoms, were also reached.

RESULTS

At the end of the study, the transcutaneous oxygen saturation values at the end of session seven were increased compared with the baseline, but this increase was not statistically significant. These values before and after each session are shown in Table 2.

Despite some reductions in albumin, fibrinogen, IgM, LDL-cholesterol, and alpha-2 macroglobulin levels during each session, no significant changes were noted at the end of treatment after a comparison with the baseline values ($p<0.05$).

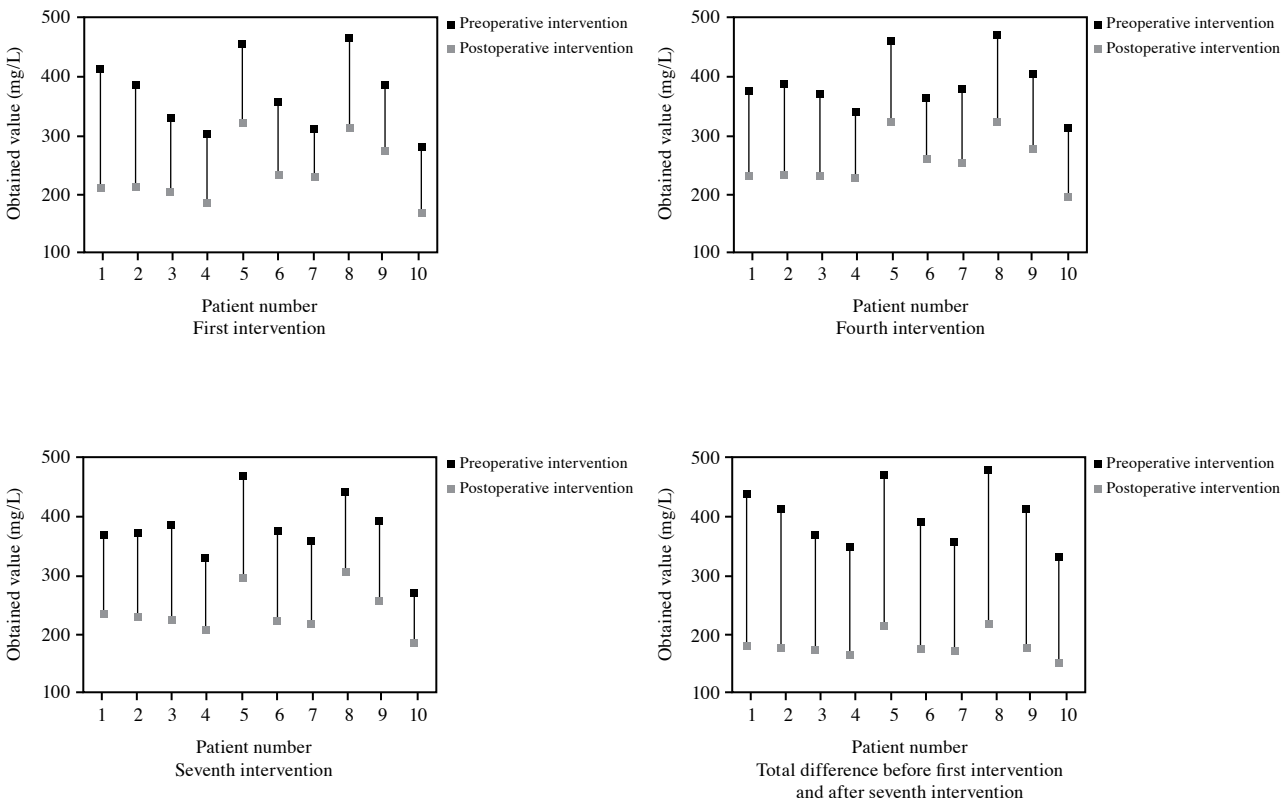

Figure 1. Changes in fibronectin levels before and after the cascade filtration procedure.

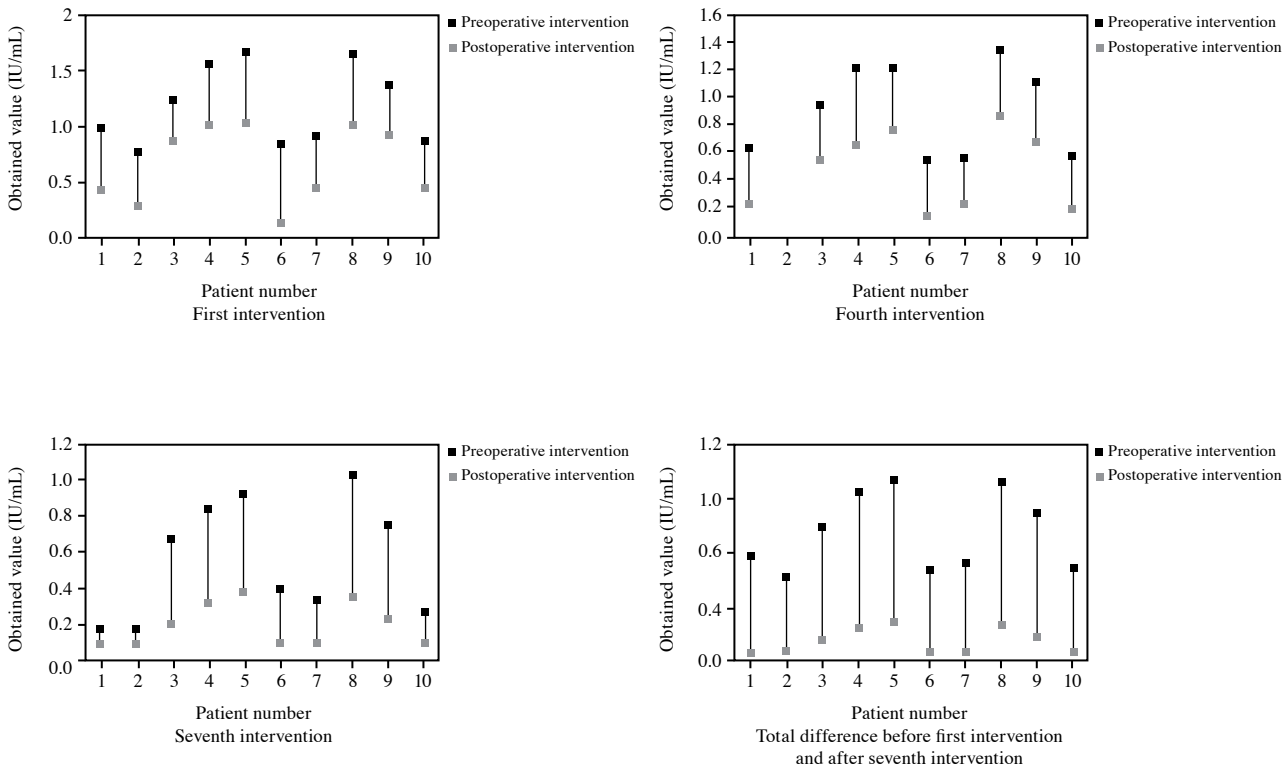

Figure 2. Changes in von Willebrand factor levels before and after the cascade filtration procedure.

Furthermore, the fibronectin levels at the end of the protocol were significantly increased when compared with the baseline levels p=0.005), and Pearson's correlation test revealed a significant decrease in vWF (p=0.003) that occurred at the end of session seven.

The laboratory results at baseline and at the end of session seven are presented in Table 3. Changes in fibronectin and vWF values are presented in Figures 1 and 2.

A significant reduction in viscosity was observed at the end of the procedure. The viscosity values before and after the procedure are shown in Table 4, and the reduction was significant according to the Pearson correlation test (p=0.019). The changes in viscosity before and after each session are shown in Figure 3.

Various degrees of improvement were noted in seven patients after examining their baseline values on the Wagner scale. After completion of the protocol, amputation at a more distal level than had been previously planned was performed on three patients. Two patients underwent below-knee amputations and one had a finger amputation.

DISCUSSION

Peripheral artery diseases often exhibit a slow progression in the extremities. Extremity pain during rest or tissue loss (unimproved ulcers or gangrene) is termed critical limb ischemia. If left untreated and if microcirculation is not improved, critical limb ischemia may progress to amputation.[10] Cascade filtration is an effective and reliable method for the management of microcirculatory disorders.[3,11] We performed a total of 70 sessions of cascade

Table 4. Viscosity values before and after the cascade filtration procedure

	Transcutaneous oxygen saturation values (mmHg)					
	Session 1		Session 4		Session 7	
Case	Before	After	Before	After	Before	After
1	1.23	1.08	1.16	1.11	1.17	1.10
2	1.33	1.16	1.18	1.10	1.11	1.07
3	1.39	1.21	1.30	1.14	1.14	1.11
4	1.24	1.14	1.32	1.16	1.23	1.08
5	1.83	1.21	1.42	1.24	1.35	1.12
6	1.15	1.08	1.16	1.07	1.15	1.05
7	1.14	1.02	1.12	1.10	1.15	1.08
8	1.15	1.12	1.16	1.14	1.15	1.14
9	1.18	1.16	1.14	1.04	1.08	1.02
10	1.14	1.12	1.13	1.12	1.14	1.10

filtration in the 10 patients in our study. We also measured the transcutaneous oxygen saturation and viscosity and monitored the serum levels of macromolecules to evaluate the effectiveness of the procedure.

Inadequate oxygenation in atherosclerotic peripheral vascular diseases leads to tissue damage. Transcutaneous oxygen saturation is an accurate and valuable parameter for measuring local extremity oxygenation. It is also a simple, reproducible, inexpensive, and useful method for the assessment of claudication in patients with peripheral artery disease and for the evaluation of asymptomatic patients in the early stages.[8,9,12-15] Furthermore, transcutaneous oxygen saturation is also a useful tool for predicting the prognosis of patients progressing towards amputation. In a prospective study involving 147 patients with a limb-threatening acute diabetic foot infection, Bunt and Holloway[16] reported that improvement rates were better in amputation patients with a transcutaneous oxygen saturation of ≥30 mmHg. Franzeck et al.[17] in a comparative study involving 69 patients with peripheral artery disease and 24 controls reported that the transcutaneous oxygen saturation measurement is a useful parameter for determining the optimal level of amputation.

In the current study, the measurement of transcutaneous oxygen saturation was performed to evaluate tissue repair as a result of improvement in the microcirculation following cascade filtration. At the end of the procedure, a statistically insignificant increase in these values was identified compared with the baseline. In general, transcutaneous oxygen saturation values of <20 mmHg are considered to be associated with irreversible tissue damage.[18] In this study, values of <20 mmHg were found in all of the patients at baseline, but in only four patients at the end of session seven. These results suggest the clinically beneficial effect of the cascade filtration procedure on tissue oxygenation.

An increase in high molecular weight plasma proteins is known to cause impairment in microcirculation by increasing viscosity. Therefore, elimination of these proteins from the plasma via the cascade filtration procedure helps to reduce this viscosity.[3,19] The relationship between atherosclerosis, which has a significant role in the etiology of ischemia of the leg, and hypercholesterolemia is also well-known. Therefore, removal of LDL-cholesterol from the plasma by apheresis techniques also plays an effective role in management.[20-23] Plasma fibrinogen and LDL-cholesterol can be reduced by up to 50%

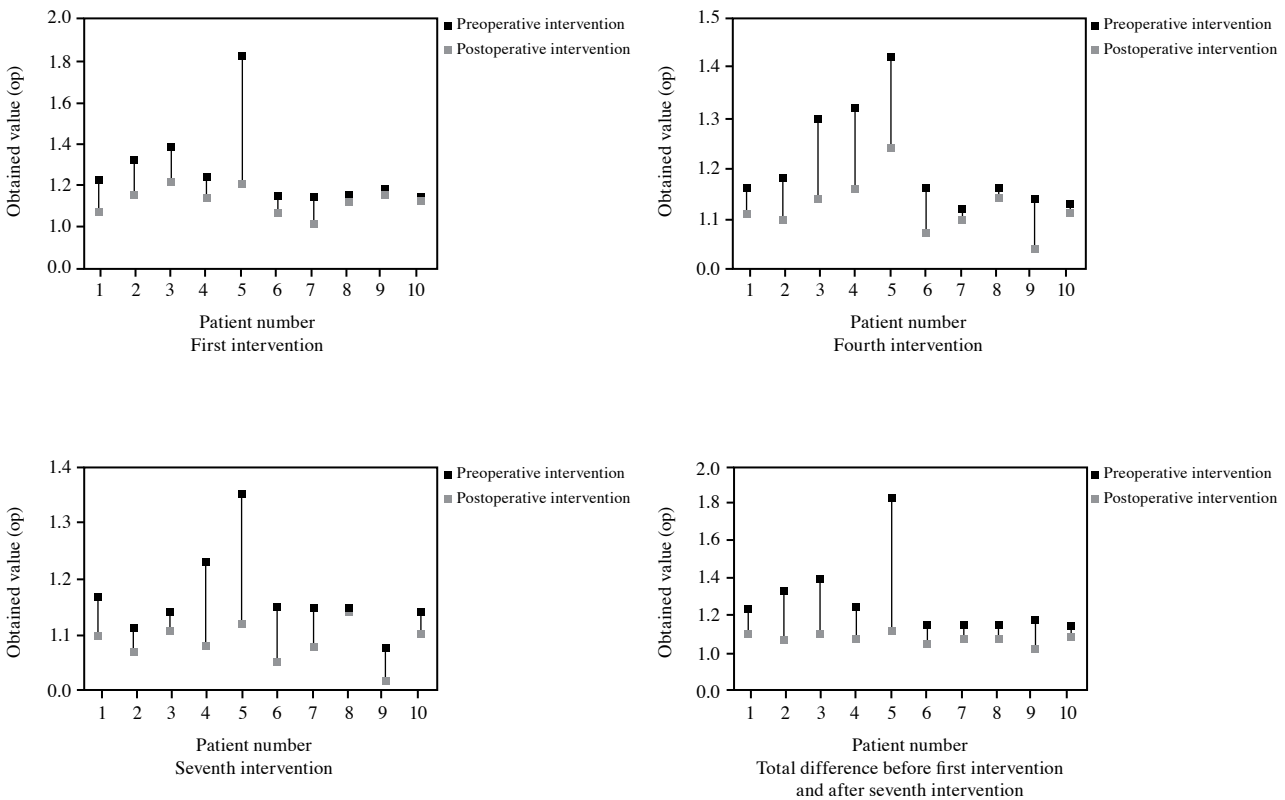

Figure 3. Changes in viscosity before and after the cascade filtration procedure.

and 60%, respectively, using the cascade filtration method.[18] In the current study, some reduction in albumin, fibrinogen, IgM, LDL-cholesterol, and alpha-2 macroglobulin levels were noted during each session period, but no significant change occurred at the end of the treatment (i.e., before the first and after the seventh sessions). Nonetheless, the viscosity levels at the end of the protocol were significantly decreased compared with the baseline values.

Various degrees of improvement were noted in seven patients, and changes were made in the more distal levels of amputation in three patients. These results suggest that cascade filtration might provide clinical benefit.

In conclusion, cascade filtration was performed in patients with peripheral vascular disease, and a significant reduction in fibronectin, vWF, and viscosity levels was demonstrated at the end of seven sessions. Larger series of studies are needed to confirm our findings; however, cascade filtration, despite its high cost, seems to be an effective treatment alternative that can limit or prevent amputation in these patients.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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