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Additional cilostazol to iloprost trometamol improves six-month outcomes in critical limb ischemia patients with resting pain: a randomized-controlled trial

İstirahat ağrısı olan kritik bacak iskemili hastalarda iloprost trometamole eklenen silostazol altı-aylık sonuçları iyileştirir: Randomize kontrollü çalışma

Suat Doğancı,[1] Erkan Kaya,[1] Murat Kadan,[1] Gökhan Erol,[1] Vedat Yıldırım,[2] Ufuk Demirkılıç[1]

[1]Department Cardiovascular Surgery, Gülhane Military Medical Academy, Ankara, Turkey
[2]Department of Anesthesiology and Reanimation, Gülhane Military Medical Academy, Ankara, Turkey

Background: This study aims to compare the efficacy of iloprost trometamol plus cilostazol combination versus iloprost trometamol monotherapy in patients with critical leg ischemia.

Methods: Sixty patients with critical leg ischemia were randomly assigned to receive either iloprost trometamol concomitant with a six-month course of cilostazol (group 1, n=30) or standard treatment with iloprost trometamol (group 2, n=30). The primary endpoints were changes in ankle-brachial index, walking distance, and score changes in the visual analog scale, and limb preservation at 24 weeks. The secondary endpoints were re-hospitalization requirement and the amount of analgesics used.

Results: There was a mean increase of 12% and 5.14% in the ankle-brachial index in group 1 and 2, respectively ($p<0.05$). Maximum walking distance at baseline and at 24 week were as follows: Group 1 baseline 43.1 m, group 2 baseline 43.5 m ($p>0.05$), group 1 at 24 week 75.1 m, group 2 at 24 week 63.8 m ($p>0.05$). The mean change in maximum walking distance in groups was 32 m (74.2%) increase from the baseline distance in group 1 and 20.3 m (46.6%) in group 2 ($p<0.05$). The visual analog scale scores at baseline were 8.4 in group 1 and 8.3 in group 2 ($p>0.05$). Twenty four-week control values were reduced to 3.5 and 5.2, respectively ($p<0.05$). One patient underwent digital amputation in group 2. After a 24-week period, seven patients in group 1 were using analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAID). Six patients in group 2 required re-hospitalization.

Conclusion: The treatment of critical leg ischemia with iloprost trometamol plus cilostazol combination therapy exhibited better results, compared to iloprost trometamol monotherapy. The combination therapy is promising in terms of the symptomatic relief and improved quality of life of the patients. This therapeutic regimen should be considered in patients in whom percutaneous intervention or revascularization are not possible.

Key words: Cilostazol; critical leg ischemia; iloprost.

Amaç: Bu çalışmada kritik bacak iskemili hastalarda iloprost trometamol monoterapisine kıyasla, iloprost trometamol ve silostazol kombinasyonunun etkinlikleri karşılaştırıldı.

Çalışma planı: Kritik bacak iskemili 60 hasta iloprost trometamol infüzyonu ile birlikte altı aylık silostazol tedavisi (grup 1, n=30) veya standart iloprost trometamol infüzyonu (grup 2, n=30) uygulanmak üzere iki gruba randomize edildi. Çalışmanın primer sonlanma noktaları ayak-bileği kol indeksi, yürüme mesafesi ve görsel analog ölçeği'ndeki skor değişimleri ile 24 haftalık sürede ekstremitenin korunmasıydı. Hastaneye tekrar yatma gereksinimleri ve analjezik ilaç kullanım miktarları da çalışmanın ikincil sonlanma noktaları idi.

Bulgular: Ayak bileği kol indeks ölçümleri açısından grup 1 ve grup 2'de sırasıyla ortalama %12 ve %5.4'lük artış olduğu gözlendi ($p<0.05$). Başlangıç ve 24. haftadaki maksimum yürüme mesafeleri: Başlangıç: grup 1: 43.1 m, grup 2: 43.5 m ($p>0.05$), 24. haftada: grup 1: 75.1 m, grup 2: 63.8 m ($p>0.05$). Grup 1'de başlangıca göre maksimum yürüme mesafesinde 32 m (%74.2), grup 2'de ise 20.3 m (%46.6) artış gözlendi ($p<0.05$). Görsel analog ölçeği skoru başlangıçta grup 1'de 8.4, grup 2'de 8.3 idi ($p>0.05$). Yirmi dört haftalık periyot sonunda bu değerler grup 1'de 3.5 ve grup 2'de 5.2'ye geriledi ($p<0.05$). Grup 2'de bir hastada parmak ampütasyonu yapıldı. Yirmi dört haftalık periyot sonunda grup 1'deki yedi hasta parasetamol ve nonsteroid antiinflamatuvar ilaç (NSAİİ) gibi analjezikler kullanıyordu. Grup 2'de altı hastada yeniden hastaneye yatış gereksinimi oldu.

Sonuç: Kritik bacak iskemisinin iloprost trometamol artı silostazol kombinasyonu ile tedavisi, iloprost trometamol monoterapisine kıyasla, daha iyi sonuçlar vermiştir. Bu kombinasyon, semptomatik rahatlama ve hastaların yaşam kalitesinde iyileşme açısından ümit vericidir. Perkütan girişim veya revaskülarizasyon seçeneği olmayan hastalarda bu tedavi rejimi akılda bulundurulmalıdır.

Anahtar sözcükler: Silostazol; kritik bacak iskemisi; iloprost.

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Correspondence: Suat Doğancı, M.D. Gülhane Askeri Tıp Akademisi, Kalp ve Damar Cerrahisi Anabilim Dalı, 06010 Etlik, Ankara, Turkey.
Tel: +90 312 - 256 30 60 e-mail: suat_doganci@yahoo.com

Peripheral artery disease (PAD) is a pathology consisting of obstruction of the arterial lumen by different factors that lead to decreased blood flow and malperfusion of the extremities.[1] Rutherford classified this disease by dividing it into categories from 0 to 6 (0= asymptomatic, 1= mild intermittent claudication, 2= moderate intermittent claudication, 3= severe intermittent claudication, 4= rest pain, 5= minor tissue loss, 6= major tissue loss). The ankle-brachial index (ABI) measurement is a simple and effective method to diagnose and classify PAD as follows: normal (ABI 1.00 to 1.29), borderline PAD (ABI 0.91 to 0.99), mild-to-moderate PAD (ABI 0.41 to 0.90), severe PAD (ABI less than 0.40), and non-compressible (ABI greater than 1.30).[2,3]

Critical limb ischemia (CLI) is a clinical condition defined as an advanced stage of PAD (category 4-6). These patients suffer from rest pain or have tissue defects (ulcers/gangrene), and the integrity of the limb is in danger. They have intolerable pain that has persisted for over two weeks along with an ankle pressure of 50 mmHg or less.[4,5] According to one study, the risk for limb loss within a year is estimated to be 70% and 95% for category 4 and 5-6 patients, respectively.[6]

Surgical and percutaneous revascularization is the treatment of choice for CLI, but conservative treatment regimens remain the only option in cases that are not suitable for intervention. Prostaglandin E1 (PGE1) and iloprost [a prostacyclin (PGI2) analogue] are the first choices among drug therapy. However, cilostazol, a phosphodiesterase III (PDE3) inhibitor with antiplatelet, vasodilator, and anti-thrombotic effects that inhibits vascular smooth muscles, decreases triglyceride levels, and increases blood flow and high-density lipoprotein (HDL) cholesterol levels, is mostly preferred in patients with intermittent claudication (IC).[3,4,7] For CLI patients, the TransAtlantic Inter-Society Consensus (TASC) II guidelines suggest that iloprost trometamol should be the standard treatment modality. Moreover, it was the only recommended pharmaceutical agent for these patients. The same guidelines also state that cilostazol is the first choice of pharmacotherapy in patients with IC, but no indication was given for CLI patients.[2]

In this study, we compared the results of category 4 CLI patients treated with both iloprost and cilostazol versus iloprost, alone in order to determine any beneficial additive effects of this two-drug combination.

PATIENTS AND METHODS

The local ethics committee of the Gülhane Military Academy of Medicine approved this study, and written consent was obtained from all patients.

Patient selection

The only inclusion criterion was admission with atherosclerotic PAD that was classified as Rutherford category 4. Exclusion criteria included hypersensitivity to any antiplatelet agent or study drugs, pregnancy, planned revascularization surgery or percutaneous intervention, contraindication to anticoagulation therapy, acute pulmonary edema, and cardiogenic shock or other severe systemic disease. In addition, patients with known bleeding disorders or liver disease, CLI with tissue defects (Rutherford category 5 and 6), or Buerger's disease were also excluded from the study.

Between August 2007 and June 2009, 81 patients with CLI were admitted to our center. However, 13 of them (16%) were classified as Rutherford category 5-6 due to tissue loss, six (7.4%) had Buerger's disease, and two others had severe systemic disease, so they did not meet the criteria for inclusion. The remaining 60 patients with Rutherford category 4 CLI were prospectively enrolled in this single-center, randomized study. A consort diagram of the study is shown in Figure 1.

After enrolling in the study, the patients were divided into two groups according to a computer-generated randomization list, with group 1 receiving therapy with both iloprost and cilostazol (24 males, 6 females; mean

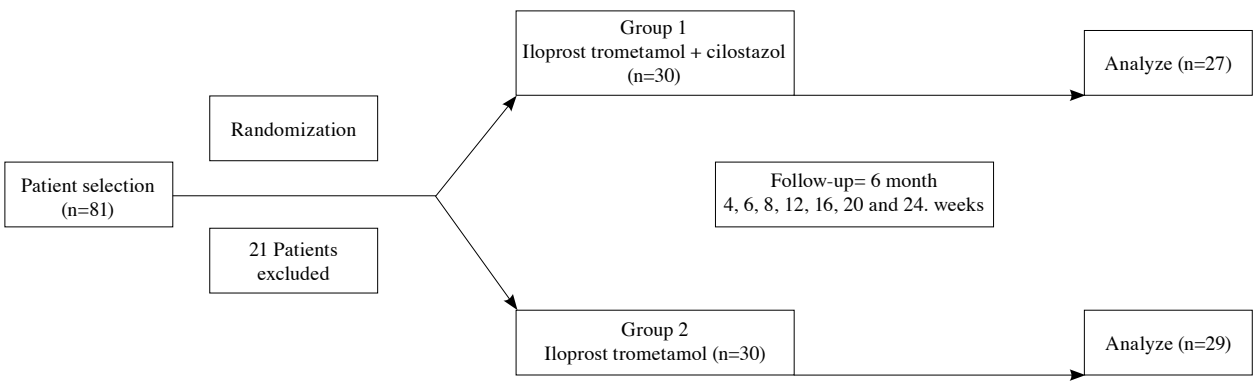

Figure 1. Consort diagram of the study.

age 60.27±15.1 years) and group 2 receiving routine therapy with iloprost alone (22 males, 8 females; mean age 60.51±13.6 years).

Endpoints

The primary endpoints of the study were changes in the ABI measurements, the maximum walking distance measured by a treadmill test, the visual analog scale (VAS), and limb preservation at 24 weeks.

The requirement for rehospitalization and amount of analgesics taken were secondary endpoints.

Study protocol and follow-up

All patients received an infusion of iloprost trometamol (0.5 to 2.0 ng/kg/min) over a 12-hour period daily for 10 days. Patients in group 1 also received cilostazol (100 mg orally, twice daily) for six months in addition to the iloprost infusion during a 24-week period.

The maximum walking distance was measured using a treadmill set at a speed of 3 km/hour at a 10% slope and was expressed as the distance the patient was able to walk due to intolerable pain.

To calculate the ABI, the ratio of the lower extremity systolic pressure to the upper extremity systolic pressure, an air-filled plethysmograph was placed on both the upper and lower limbs to record the pulse volume and segmental pressure by continuous Doppler. The VAS records pain levels, and the patients were instructed in how to accurately asses their pain using this 10-step scale (0= no pain, 10= greatest imaginable pain) along with how to use the patient-controlled analgesia (PCA) devices (Abbott Pain Management Provider, Abbott Laboratories, Abbott Park, Chicago, USA).

The number of patients who required amputation and who needed rehospitalization were recorded during the study period together with the amount of analgesic drugs that each patient used.

The patients were examined before the study, and follow-ups were scheduled at week four, eight, 12, 16, 20, and 24 of the treatment course.

Risk factor modification

All patients received clopidogrel 75 mg/day and atorvastatin 40 mg/day. Additionally, 47 patients who smoked were encouraged to quit. The regulation of each patient's diet, blood glucose levels, and blood pressure was also a part of the modification strategy. While 18 out of 27 diabetic patients received sulfonylurea and biguanide (or its derivatives), the remaining nine also received insulin treatment. Angiotensin-converting enzyme (ACE) inhibitors, drugs containing hydrochlorothiazide, angiotensin receptor blockers (ARBs), beta blockers, and calcium channel blockers were used to control hypertension, and all patients with pulmonary disease or renal dysfunction continued their current therapy.

Pain control

To relieve pain, all patients were connected to a PCA device which was set to deliver continuous doses of morphine sulphate (0.3 mg/h basal infusion; 1 mg as an intravenous bolus with a 15-minute lockout interval) during the hospitalization period. In patients who did not require the morphine sulphate bolus for more than four hours, the infusion was stopped, and a combination of paracetamol 500 mg and codeine 30 mg was started and given three times a day. The amount of morphine used was recorded for both groups, and at

Table 1. Demographic data of patients

Parameters	Group 1 (n=30)			Group 2 (n=30)		
	n	%	Mean±SD	n	%	Mean±SD
Age (years)			60.27±15.1			60.51±13.6
Gender						
Male	24	80		22	73.3	
Female	6	20		8	26.7	
Smoking history	25	83.3		22	73.3	
Diabetes mellitus	13	43.3		14	46.6	
Hypertension	20	66.6		18	60	
Hypercholesterolemia	13	43.3		13	43.3	
Coronary artery disease	14	46.6		15	50	
Carotid artery disease	4	23.3		3	30	
Chronic obstructive pulmonary disease	5	16.6		6	20	
Renal dysfunction	1	3.3		1	3.3	

SD: Standard deviation.

each follow-up, the patients were questioned regarding their use of analgesics.

Statistical analysis

Statistical analysis was performed by using the Statistical Package for Social Sciences (SPSS Inc, Chicago, Illinois, USA) Windows version 15.0 software program. Changes in maximum walking distance, ABI measurements, VAS scores, and the amount of opioids used were compared using the Mann-Whitney U test, and a *p* value of <0.05 was considered to be significant.

RESULTS

The demographic and clinical details of all 60 patients are presented in Table 1. There were no significant differences between the baseline characteristics of the two groups.

When the patients were evaluated, we identified seven risk factors [smoking, diabetes, hypertension, hyperlipidemia, coronary heart disease, carotid artery disease, chronic obstructive pulmonary disease (COPD), and renal disease]. When the coexistence of these risk factors was assessed, we found that 39 of the patients had two of these risk factors, 35 had three, 15 had four, and 15 had five coexisting risk factors.

Primary end points

Walking performance was assessed with a treadmill, and this progressively increased in both groups (Figure 2). The changes in the maximum walking distance in group 1 were greater than that of group 2 at 24 weeks. The mean maximum walking distance was 43.1 meters (m) in group 1 and 43.5 m in group 2 at baseline (p>0.05) and 75.1 and 63.8 at week 24, respectively (p>0.05). When we evaluated the changes of these parameters from the baseline to week 24, a statistically significant difference was found between the groups, with a distance of 32 m in group 1 (74.2%) versus 20.3 m (46.6%) in group 2 (p<0.05). Among the observed cases, the walking distance in one patient in group 1 and two patients in group 2 got worse or remained unchanged after 24 weeks of therapy.

The VAS showed a significant decrease at 24 weeks in both groups (Figure 3). The mean VAS at baseline was 8.4±1.9 and 8.3±1.7 in groups 1 and 2, respectively. However, at the end of the 24 weeks, the mean VAS was 3.5±0.6 and 5.2±0.7 in groups 1 and 2, respectively. There was a statistical difference between the two groups beginning from the fourth week (p<0.05). When we compared the changes in the VAS points at 24 weeks and at baseline, there was a decrease of 58.4% in group 1 and 32.7% in group 2 (p<0.01).

The mean ABI improved slightly in both groups over the 24-week period. Group 1 progressed from 0.389±0.02 at baseline to 0.436±0.04 at week 24, and group 2 moved from 0.389±0.02 at baseline to 0.409±0.02 at week 24 (p>0.05) (Figure 4). When these changes were evaluated, there was a 12% improvement in group 1 at 24 weeks and a 5.14% improvement in group 2 (p<0.05).

There was one digital amputation in group 2, but none occurred in group 1.

Secondary end points

Two patients (6.6%) in group 1 and six patients (20%) in group 2 needed rehospitalization. During this time, iloprost was administered to all of the patients for 10 days. Two patients in group 2 were rehospitalized twice. One of them needed a digital amputation as mentioned before, and the other one needed consecutive dressing and hyperbaric oxygen treatment due to a

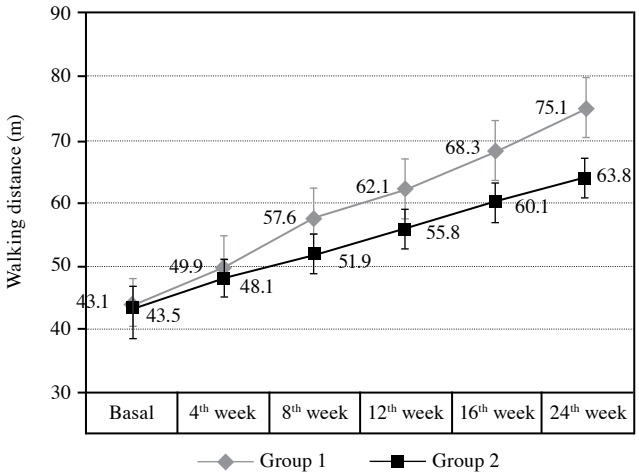

Figure 2. Changes in the maximum walking performance of the patients.

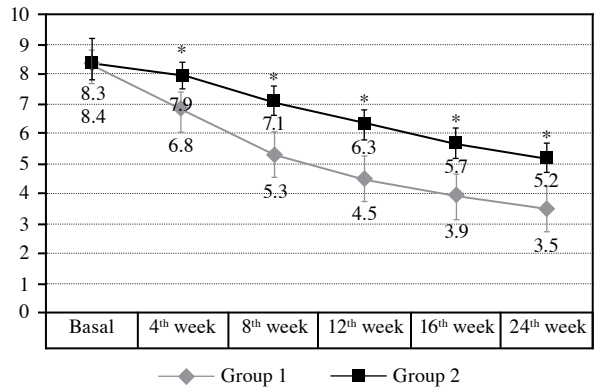

Figure 3. Changes in the patients' visual analog scale (VAS) scores. * p<0.05.

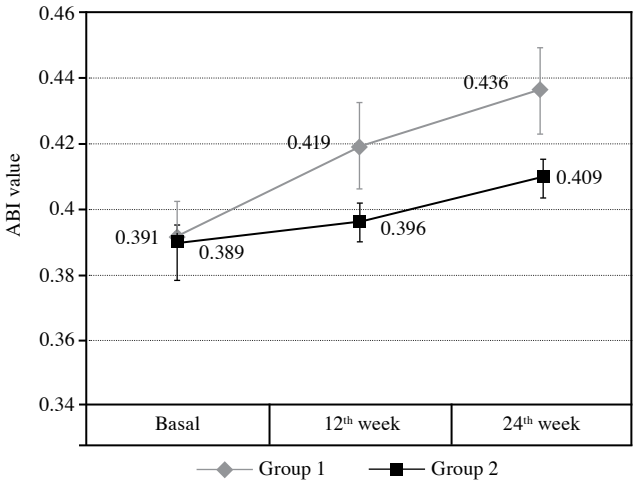

Figure 4. Changes in the ankle-brachial index of the patients.

traumatic superficial ulcer, which subsequently healed completely.

At baseline, all of the patients in both groups were taking analgesics either periodically or regularly for pain. There was a significant decrease in the use of opioids in both groups between the first half and second half of the hospital course. In group 1, 76 mg of morphine sulphate was needed for the first five days while only 8 mg was needed during the second five days. A similar decrease was seen in group 2 as 87 mg of morphine sulphate was needed in the first five days of treatment while just 25 mg was needed in the second five days (Figure 5). At the end of the study, seven patients from group 1 and 15 patients from group 2 were detected to have various analgesic requirements.

Side effects of cilostazol treatment

Seven patients (23.3%) suffered from minor side effects due to cilostazol, including erythema, palpitations, nausea, diarrhea, headaches, and vertigo. These usually disappeared spontaneously, but in four patients, the headaches only disappeared after decreasing the cilostazol dosage from 100 mg to 50 mg twice daily.

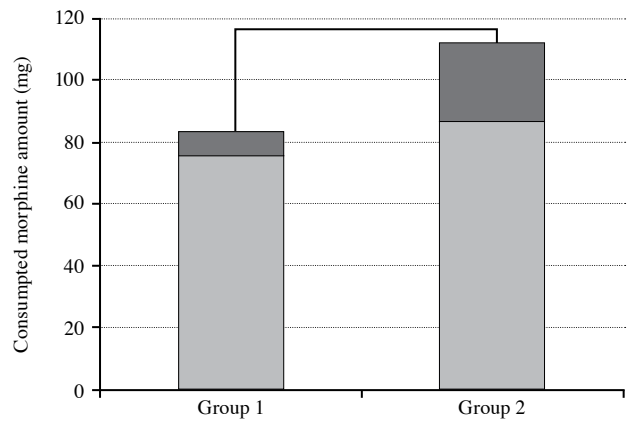

Figure 5. Ten days in hospital morphine consumption.

Follow-up data

One patient in group 1 and one patient in group 2 died due to a cerebrovascular event and myocardial infarction (MI), respectively. Another patient in group 1 discontinued treatment without providing any reason. In addition, one patient from group 1 who underwent a lumbar sympathectomy at another center was also excluded from the study.

DISCUSSION

Critical limb ischemia is a type of peripheral arterial disease and manifests with ischemic rest pain, ulcerations, and gangrene. In patients with CLI, arterial perfusion is severely compromised and is not sufficient to provide the metabolic needs of the extremity despite collateral revascularization and compensatory vasodilatation. As a result, patients with CLI are usually functionally disabled and also have a high risk of limb loss and other complications.[8] The prevalence of CLI is not exactly known, but its incidence is 300/1,000,000 per year as calculated using IC statistics.[9] The risk factors for CLI include atherosclerosis, diabetes mellitus (DM), smoking, and age.[9] In our group of patients, we discovered that many CLI patients had two or more risk factors. From this point of view, it can be extrapolated that patients with CLI represent a group that is very difficult to treat. Physicians should not only treat these patients for peripheral arterial disease, but also should treat the patient as a whole.

In one study, the authors determined that there are 150,000 leg amputations each year due to CLI in the United States.[10] The prognosis and survival is not promising as 20% of these patients die within a six-month period. They also discovered that 35% live but require an amputation. The remaining 45% survive without any amputation.[9]

Immediate hospitalization right after the diagnosisis is necessary for those with CLI, and revascularization is the primary treatment option. Unfortunately, many of these patients do not have suitable vascular structures, which leads to difficult or even hazardous percutaneous interventions. Therefore, medical treatment and physical therapy remain the only treatment options for the physician and the only hope for these patients.[5]

The treatment goals for CLI are to provide pain relief, promote wound healing, and preserve limb function while minimizing the overall cardiovascular risks. When

these are achieved, they help maintain independence and quality of life. Anticoagulants and antiplatelet agents along with prostanoids and their derivatives have been used for treating CLI, but none of these regimens produced significant or long-term improvement.[11] According to the TASC II guidelines for the management of patients with peripheral arterial disease, previous studies involving parenteral administration of PGE1 or iloprost for CLI have suggested that there was improved relief of rest pain, healing of ischemic ulcers, and a reduction in amputations (Level of evidence A).[2] However, these benefits are limited to a small percentage of patients.[2] Ruffolo et al.[11] determined that intravenous iloprost infusion is a favorable choice in the treatment of CLI and that it shows beneficial results regarding major amputations. Parenteral infusion of iloprost for seven to 14 days has been the treatment of choice in CLI patients who are not suitable candidates for surgery for many years in our department.

Cilostazol was approved for the treatment of peripheral occlusive arterial disease in Japan in 1988. After 11 years, The United States Food and Drug Administration (FDA) also approved it, and cilostazol began to be used in daily practice for the treatment of IC.[8] The precise mechanism of cilostazol is not fully defined, but it is known that it inhibits cyclic adenosine monophospate (cAMP) phosphodiesterase III, which leads to a decrease in phosphodiesterase activity and a suppression of cAMP degradation. Thus, the cAMP levels of platelets and blood vessels are increased, resulting in an inhibition of platelet aggregation and vasodilatation.[12] In addition to these effects, cilostazol also increases plasma HDL cholesterol levels and decreases plasma triglyceride levels, which indirectly helps prevent atherosclerosis.[13]

Several studies have clearly documented that treatment with cilostazol increases arterial perfusion and eliminates the symptoms of superficial ulcers while improving their healing rates.[14] In a previous study, Money et al.[15] documented a statistically significant increase in the ABI of patients with IC who were treated with cilostazol compared with those treated with a placebo (0.64-0.70 in the cilostazol group versus 0.68-0.69 in the placebo group; $p<0.0125$). Today, according to the TASC II guidelines, cilostazol treatment lasting for three to six months should be the first choice in pharmacotherapy in order to eliminate the symptoms of claudication. The same guidelines declare that there is an improvement in "treadmill exercise performance" and quality of life with cilostazol treatment (Level of evidence A).[2] Even though there is sufficient information to suggest that cilostazol should be used for patients with IC, there has not been any recommendation for its usage with CLI.[2] However, to be fair, there are only a few reports of the benefits of cilostazol with regard to CLI in the literature.[8,9]

Since the introduction of cilostazol in 2007 in our country, we have achieved remarkable results in IC treatment, leading us to hypothesize that adding it to the iloprost infusion could provide increased benefits in these patients. None of the patients in our study were suitable for intervention or surgery; hence, medical therapy was their only option. The use of cilostazol yielded positive results, even during the hospital stays of our patients. There was a 68 mg difference in the amount of morphine sulphate needed between the first and second half of the hospitalization course in group 1 and a 52 mg difference in group 2 ($p<0.05$).

Another definitive conclusion concerned the maximum walking distance. The difference in maximum walking distance among the groups was not statistically significant; however, the increase in the walking distance from the patients' baseline through week 24 was statistically significant, demonstrating the effectiveness of cilostazol treatment. At 24 weeks, the mean improvement in maximum walking distance among group 1 was 32 m, showing a 74.2% increase from the baseline distance, and group 2 increased their maximum walking distance by 20.3 m, revealing a 46.6 % increase from the baseline ($p<0.05$).

The other important primary end point of our study was associated wtih ABI as it was revealed that cilostazol improved ABI values in CLI patients. There was an increase in the mean ABI levels of 0.047 (12.0%) in group 1 and 0.02 (5.14%) in group 2, and this was statistically significant ($p<0.05$). If we consider the 0.4 level to be the cut-off point for critical ischemia, although there was slight increase in our study, it was shown that patients who passed by this cut-off level no longer had critical ischemia.

The VAS also showed a significant improvement in both groups beginning in the fourth week, but the decrease in group 1 was greater than that in group 2.

The treatment of CLI is still quite difficult and laborious and often has disappointing results.[11] The continuous pain, immobilization, and risk of amputation create an onerous psychological state for these patients; therefore, even the slightest positive result would provide them with some hope. Hence, using cilostazol in such patients could be promising, even if there are currently not enough studies that show its beneficial effects and even if there are no guidelines

which recommend this treatment at the moment. Indeed, it is true that there are only a few studies in the literature that underlie the effects of cilostazol in CLI patients, but we hope that our study can serve to initiate more research about this topic.

In conclusion, the patients who underwent medical therapy with cilostazol in combination with iloprost therapy in our study showed improvement in their symptoms and maximum walking distance. An amelioration of ABI was also seen. Due to these promising results, we share the opinion that cilostazol should be used as a routine treatment option in this group of patients. However, further investigations with larger groups over a longer period of time would be helpful in determining the evidence level of this drug in CLI treatment.

Declaration of conflicting interests

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

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