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Medical Therapy In Peripheral Artery Disease Using Pentoxifylline

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Abstract

In addition to its anti-inflammatory properties, pentoxifylline is an active methyl-xanthine derivative with many other advantages. Many dermatological and non-dermatological diseases respond well to pentoxifylline, which has been studied extensively. A safe and cost-effective alternative to the standard medication, it has been utilised both as a main and adjuvant treatment. Pentoxifylline is discussed in this article as a review of the literature, with an emphasis on different critical elements. A thorough history and physical examination are critical in the diagnosis of PAD, but they are hampered by a lack of consistency in their sensitivity and specificity. You may quickly confirm your diagnosis and stratify your risk with noninvasive office-based diagnostics such as an ankle-brachial index. To evaluate disease progression and forecast cardiovascular and cerebrovascular mortality, the ankle-brachial index is useful. It has a strong correlation with disease severity and functional symptoms and may be utilised to do so. Following a diagnosis of PAD, treatment focuses on risk factor reduction, symptom alleviation, and secondary prevention using antiplatelet medications.

Key words: Pentoxifylline, peripheral artery disease (PAD), diagnosis

1. Introduction

Peripheral artery disease (PAD) epidemiology is well understood and linked to variables such as age, diabetes mellitus, and cigarette smoking. There is an estimated prevalence in the United States of 7.2 million people who are afflicted, according to recent data from the National Health and Nutrition Examination Survey (NHANES). 1 Because of the underlying atherosclerotic disease process and overall under treatment of PAD risk factors, these patients have a significantly elevated risk of death from any cause.

It is a methyl-xanthine derivative having anti-inflammatory properties, such as phentoxifylline. Despite many studies showing pentoxifylline's efficacy for a wide range of dermatological diseases, the FDA has only authorised it for use in the treatment of intermittent claudication..

Pentoxifylline's chemical formula is C13H18N4 O3, and its systematic name is 3,7-dimethyl-1- (5-oxohexyl)-3,7-dihydro1H-purine-2,6-dione. To visualise it, go no further than Figure 1.

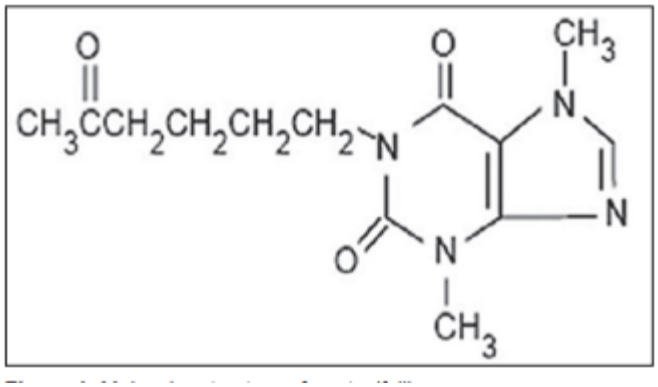

Figure 1: Molecular structure of pentoxifylline

Patients with peripheral artery disease are often prescribed antithrombotic medications. That's the subject of this article (PAD). Other vascular beds are more likely to develop atherosclerosis in people with PAD. MI and stroke are the main causes of death and morbidity for patients with PAD, thus avoidance of vascular events and mortality is a key benefit of antithrombotic treatment in this patient group, as it is in patients with CAD. Total mortality, MI, stroke, and significant nonfatal extracranial bleeding are all outcomes that patients care about. These are the same outcomes used to make CAD and stroke prevention recommendations. Antithrombotic treatment has been shown to improve PAD-specific outcome, although further research is needed (eg, rest pain of the limbs, quality of life, or amputation).

After peripheral bypass graft surgery or percutaneous endovascular treatments, studies have evaluated antithrombotic therapy with graft patency or reocclusion as the main end goal. Amputations and quality of life are seldom recorded results for patients;therefore, they are substitutes.

Antithrombotic treatment has both favourable and negative effects in the following patient categories or groups: Asymptomatic PAD patients, symptomatic PAD patients (including claudication or critical [chronic] limb ischemia and rest pain, or prior peripheral arterial revascularization), acutely ischemic patients (including those who are at risk of loss of limb), patients following peripheral arterial revascularization, and people with asymptomatic and symptomatic carotid stenosis are included. For each question, the kinds of studies examined are listed in Tables 1 and S1, which define the question definition (i.e. population, intervention, comparator, and result). Additional tables not included in the main article may be found in an online data supplement denoted by a "S" before the table number.)

2. Literature Review

It's been a while since I've written anything about Fan, but here's what I've come up with: (2014), Radiation treatment for oral cavity cancer may cause osteoradionecrosis (ORN) of the jaw. Surgical methods, hyperbaric oxygen therapy, and combination therapy with pentoxifylline and tocopherol have recently been proposed as alternatives to antibiotic prescription. The definition and classification of osteoradionecrosis, its aetiology and pathophysiology, previous treatment options, oral and maxillofacial complications of radiotherapy, basic information on pentoxifylline and tocopherol, recent reports on pentoxifylline and tocopherol combined therapy, and, finally, ORN-induced animal models and future approaches will be discussed in this review article.

The authors of this article are: Bhambal, A.M; Bhambal, A; Shukla, U.S; and others (2019), Background: There is evidence to suggest that the vasodilating property of pentoxifylline, a methylxanthine derivative, helps to enhance mucosal vascularity. These researchers set out to see what impact pentoxifylline (Trental) has on oral submucous fibrotic disease development. The study's goal was to see

how well the medication pentoxifylline worked in treating OSMF and to compare the results from before and after therapy. Methods: Research Plan: As case-control research, this investigation included a Control Group that was given 400 mg of pentoxifylline three times daily as coated, long-acting tablets for a period of three months, compared to a Study Group. In all, 80 instances of oral submucous fibrosis were included in the research (40 test patients and 40 controls). At the conclusion of the test period, there was 100 percent agreement. Two of the participants in the research group had mild dizziness and stomach discomfort as the only side effects. Nonparametric methods such as the Chi-Square test and the Mann-Whitney test were used to calibrate the follow-up data at each visit in relation to one another and to baseline values. Objective criteria such as mouth opening (u value =1.137, p = 0.260), tongue protrusion (u value = 0.262, p = 0.794), and cheek flexibility (u value =0.990, p = 0.326) showed significant improvements. Aside from difficulties swallowing and speaking, other symptoms included a burning feeling in the mouth (a U value of 2.673, a p value of 0.008) and discomfort while opening the mouth (a U value of 4.320, a p value 0.0001). Conclusion: Pentoxifylline was shown to be an effective supplementary treatment for oral submucous fibrosis when used as part of a regular management regimen.

Parenti CEF and Bueno Filho R. Abbade LPF in 2020, Frade MAC in 2020 and Pegas JRP in 2021 Background: Numerous adults are affected by chronic leg ulcers, which may have a major financial and social effect due to the time lost from work and other obligations as well as the cost of social security benefits as well as the lowered quality of life. A good outcome is dependent on having the right diagnosis and treatment plan in place. The goal is to compile the expertise of Brazilian dermatologists and evaluate specialist literature to provide diagnostic and treatment guidelines for the most common forms of chronic leg ulcers. In order to achieve an agreement on the diagnosis and treatment of chronic leg ulcers, the Brazilian Society of Dermatology selected seven experts from six university centres with expertise in the condition. The most frequent causes of chronic leg ulcers were examined using the modified DELPHI approach, and then the most current literature was evaluated based on the greatest scientific evidence.

Mulk, B. S., Deshpande, P., Velpula, N., Chappidi, V., Chintamaneni, R. L., and Goyal, S. (2001). (2013). Background: Oral submucous fibrosis is a precancerous disease of the oral cavity that is frequently seen in Asian nations due to an insidious habit linked with it. Aside from steroids, which have been the mainstay in treating the disease, several other therapeutic methods have been tried. In order to compare the effectiveness of spirulina and pentoxyfilline in oral submucous fibrosis, this research evaluated their efficacy. Sources and Procedures: Fourty Clinically diagnosed patients with oral sub mucosal fibrosis were randomly assigned to one of two groups, each with 20 patients. The first group was given Pentoxyfilline, whereas the second was given Spirulina for a three-month period of time. As well as adverse effects, the effectiveness was evaluated using vernier callipers, visual analogue scales, and metric scales for things like mouth opening, burning feeling, and tongue protrusion. Results were derived using the student's t-test. All three measures, namely mouth opening, burning sensation, and tongue protrusion, exhibited statistically significant results (p=0.000) for the Pentoxyfilline and Spirulina groups. For mouth opening (p=0.35) and tongue protrusion (p=0.25), statistically insignificant findings were obtained when comparing the two medications. However, a statistically significant difference was seen in the subjective parameter of burning sensation (p=0.04).In contrast to the Spirulina group, the pentoxyfilline group had side symptoms such as stomach bloating, nausea, and gastritis. Treatment of Oral sub mucosal fibrosis with the newer medicines Pentoxyfilline and Spirulina showed encouraging outcomes. It was shown that spirulina was better to pentoxyfilline in treating oral submucous fibrosis (OSMF) and had no adverse effects. It was also shown to be more effective in reducing the sensation of burning, making it a viable treatment option for OSMF patients with very severe subjective symptoms.

Naresh Prabhu, Srinivasa Rao, Srinivasa Kotrashetti, and colleagues (2015), What Is My Goal? Every element of illness research is difficult, regardless of the condition. Occurrences like oral submucous fibrosis (OSF), which has the potential to become malignant, represent a problem in our field since there is no effective therapy. To find out whether pentoxifylline (PTX) usage affects the clinical and histopathologic course of OSF, researchers conducted this study. Using a computerized randomization procedure, 30 clinically proven OSF patients were divided into two groups according to their OSF status. The medication PTX was given to patients in group I in addition to other standard treatments. Only conventional treatments were recommended for individuals in Group II. The following parameters were studied using pre- and post-treatment biopsies: There are four factors to consider: micro-vascular density (MVD), blood vessel area percentage (AVA), fibrosis severity (F), and inflammatory components (I). Results: 1. There was no change in pre- and post-treatment MVD between groups I and II. Pre- and post-treatment biopsies in group I showed substantial differences in the average area % occupied by blood vessels. 3.When mouth opening and tongue protrusion were measured, neither group showed any progress on its own or when compared to the other. However, pre- and post-treatment assessments of burned mucosa revealed substantial improvement in both groups. The use of pentoxifylline in the treatment of OSF patients is not advised due to the lengthy administration duration and uncertain efficacy.

3. Results and Discussion

PAD has been found in 300 individuals. Seven individuals were excluded from the research because their ABI was more than 1.4. As a result, the study comprised 150 people. People aged 18 to 102 were included in the study (mean: 44.9 16.4 years).

The present study is the most comprehensive study to date on the prevalence of PAD in a Brazilian population. In the study's sample of 150 people, PAD was found in 1,05 percent of cases. The frequency increased considerably as people aged, reaching a maximum of 5.2% in the 70+ age group. Smokers were more likely to have PAD as well as being older, heavier, and less physically active. Risk factors found in the study population were age (odds ratio [OR]=1.08), smoking, sedentary lifestyle (OR =3.75), and diabetes mellitus (OR =3.17).

Table 1: PAD prevalence by decade in men and women

Age (n)	PAD overall prevalence n cases (%)	PAD prevalence men n cases (%)	PAD prevalence women n cases (%)
Below 30(30)	1 (0.3)	1 (0.6)	0 (0)
31 - 40 (20)	0 (0)	0 (0)	0 (0)
41 - 50 (35)	0 (0)	0 (0)	0 (0)
51 - 60 (15)	3 (0.9)	1 (0.8)	2 (1.1)
61 - 70 (20)	7 (3.8)	2 (2.5)	5 (4.8)
Above 70 (30)	6(5.2)	3(5.4)	3(5.0)
PAD: peripheral artery disease.			

The prevalence of PAD increased after the fifth decade, peaking at 70, and reaching 5.2%. Only one case of PAD was discovered in someone under the age of 30. In the next decade, PAD has become more common, as seen in Table 1.

Over the age of 50, the frequency of PAD was found to be 2.6%. In line with expectations, the Alter gene was independently related to a diagnosis of PAD in both the present and previous studies. The low incidence of PAD found in the present study may be partly explained by the young average age of participants, the participation of volunteers as young as 18 years old, and the fact that the majority of volunteers (62.1 percent) were under the age of fifty. We also found a greater than average prevalance of PAD among individuals above the age of 70 in our sample (n=116).

Intermication Treatment with Pentoxifylline And Cilostazol:

Pentoxifylline versus cilostazol

Only one study compared cilostazol to pentoxifylline, and that was in 2000. Since then, the company has gathered more data. a Six hundred and eighty-eight patients with stable moderate to severe IC were randomly assigned to receive either cilostazol 100 mg twice daily, 400 mg pentoxifylline three times daily, or a placebo for a period of twenty-four weeks. As well as achieving ACD, the study sought to see whether patients' quality of life and ability to walk improved after completing treatment, as measured by surveys. This study showed that the ACDs of patients in the Cilostazol group were greater than those in the Pentoxifylline group and placebo group, respectively, with a mean change from baseline at week 24 of (54%) (30%) (34%), (p0.001). There was no statistically significant difference between the pentoxifyllin and the placebo groups.

There was a significant difference between pentoxifylline and placebo recipients in ICD (p=0.07) at the end of the study, but not between pentoxifylline and cilostazol recipients (p=0.02) (74 m, p=0.02) (57 m, p=0.0001). Cilostazol (0.04 difference) and pentoxifyllin (0.05 difference) patients, but not placebo recipients, got ABPI after 24 weeks and improved somewhat from baseline. The walking distance and speed values did not differ substantially across the groups in terms of quality of life (e.g. physical function, physical pain, physical role). Patients using cilostazol have reported greater headaches, diarrhoea, atypical faeces, and palpitations (p 0.001) than those taking pentoxifylline (p 0.001). However, palpitations details have not been provided, and no adverse effects have been seen (other than every four weeks evaluated). Patients receiving cilostazol (16%) and pentoxifylline had withdrawal of adverse effects at the same rate (19 percent). There were two deaths in the cilostazol group, three deaths in the pentoxifyllin group, and one death in the placebo group.

Adverse effects

These two drugs are generally well tolerated. The disease's most common side effects include dyspepsia, diarrhoea, nausea, headaches, and dizziness in the gastrointestinal tract and CNS. Even though it's rare, both drugs have also been linked to hypotension and edoema, according to research. Clinical investigations on Pentoxifylline have used either commercially available extended-release tablets or instantly released capsules (only used in studies). The incidence of digestive and CNS side effects was higher in capsule studies than in tablet trials.

Place in therapy

Even while pentoxifylline and cilostazol may alleviate symptoms, PVD-specific IC therapy is required. Smoking, diabetes, high blood pressure, and hypercholesterolemia are all risk factors that need to be

addressed. They'll help prevent heart disease and mortality while also slowing the spread of IC and PVD via these preventative measures. A patient's normal diet may also benefit from include the exercise.

Coronary Artery Study of Prediagnosed Patient from Ayurvedic View

Table 2 Total Patients

Sex	No. ofpatients	Percentage
Male	92	61%
Female	58	39%
Total	150	

The entire number of patients is shown in this table. There are 61% male and 39% female.

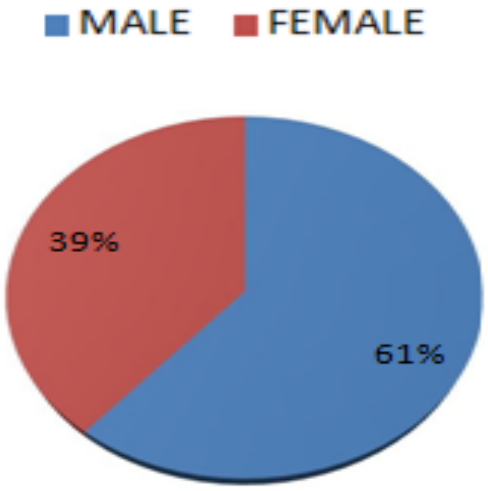

Figure 2: Distributions of Patients

Response to pentoxifylline

The research had one hundred and thirty participants. No significant changes occurred in arterial hemodynamics in any of the study's patients from its beginning to its end. There was no discernible change in hemodynamic parameters. It had been six weeks since the medication had been stopped because of gastrointestinal side effects in six patients (5 percent), and its efficacy had yet to be determined. After 7.2 + 1 month, no significant clinical improvement was seen in 88 patients (67 percent). Thirty-six of these patients stopped taking the medication before their final follow-up visit because they saw no improvement and the cost was prohibitive.

Table 3 Response to pentoxifylline

Response	No. of patients	%	Follow-up (mo)
No improvement;	78	67	7.2 --+- 1.0
patient stopped medication	36	28	
Initial response, then none	13	10	14.1 +- 2.3
Significant improvement	23	17	11.6 -+ 2.0

Claudication improved early on in 13 people (10 percent) with 14.1 + 2.3 months, but only for two to three months. These patients asked to stop taking the medication at the prior appointment for monitoring. There were 23 patients (17%) who reported complete relief from their walking difficulties after taking the medication, and their lives had returned to normal as a result.

Table 4 Severity of clinical symptoms and result with pentoxifylline

Severity of symptom	AAI ~	No. of patients	No. improved	%
Mild to moderate	0.49	85	16	19
Severe	0.39	45	7	16

About the 85 individuals who received the medication, 65 had heard of it through television commercials, family members, or their physicians. This group's resting AAI value was an average of 0.49. Pentoxifylline provided a favourable long-term response in 16 of the patients (or 19 percent).
The claudication was severe in 45 of the individuals. Some people can only walk about 50 yards before their symptoms worsen and they are severely limited in what they can do. As a result, the average AAI for this group (p 0.01) was significantly lower than the AAI for the mild to moderate group. Pentoxifylline provided a satisfactory clinical result for seven of the people studied (16 percent) (Table 4).

Effect of clinical symptoms on results

Claudication was found to be mild to severe in 85 of the patients. Leg pain from strenuous activity was a major hindrance in their day-to-day lives. There were things that were prohibited, such as mowing the lawn, going on vacation, walking through airports, or participating in strenuous sports like tennis or skiing over long distances. Grocery shopping, schoolwork, and golfing took longer, but they were all doable. This group's long-term prospects worried a lot of people.

Diagnostic Evaluation Of Patients With Peripheral Arterial Disease:

Ankle pressure measurements (ankle-brachial index)

Patients with suspected PAD are routinely evaluated by measuring the pressure in their ankle arteries. When measuring blood pressure, the most typical technique is to utilise a 10–12 cm sphygmomanometer band placed just above ankle level and a Doppler device to measure the leg's posterior tibial and dorsalis pedis arterial blood pressures (Fig. 3). The ankle-brachial index is created by normalising these pressures to the greater brachial pressure in each arm (ABI). The index leg is often thought to as the one with the lowest ABI. The ABI offers a lot of useful data. The presence of hemodynamically significant occlusive illness between the heart and ankle is confirmed by a decreased ABI in symptomatic individuals, with a lower ABI reflecting higher hemodynamic severity of occlusive disease. Patients with activity-related leg discomfort of non-vascular reasons will have a normal ankle pressure at rest and after exercise, which means the ABI may help with differential diagnosis. PAD individuals without conventional claudication (asymptomatic or with symptoms that aren't typical) had lower ABIs, which are linked with worsening of their limb function.
The ABI should be used as a standard measurement in all primary care settings. PAD was shown to be prevalent in 29 percent of those over the age of 70 when screening individuals aged 50 to 69 years who

either had diabetes or a smoking history was applied to this population. This varies from study to study, but it's substantial enough that reporting guidelines need a change of 0.15 in an isolated measurement to be deemed clinically relevant, or a change of 0.10 when linked to changes in clinical status. At rest, a blood pressure reading of 0.90 indicates the presence of PAD.

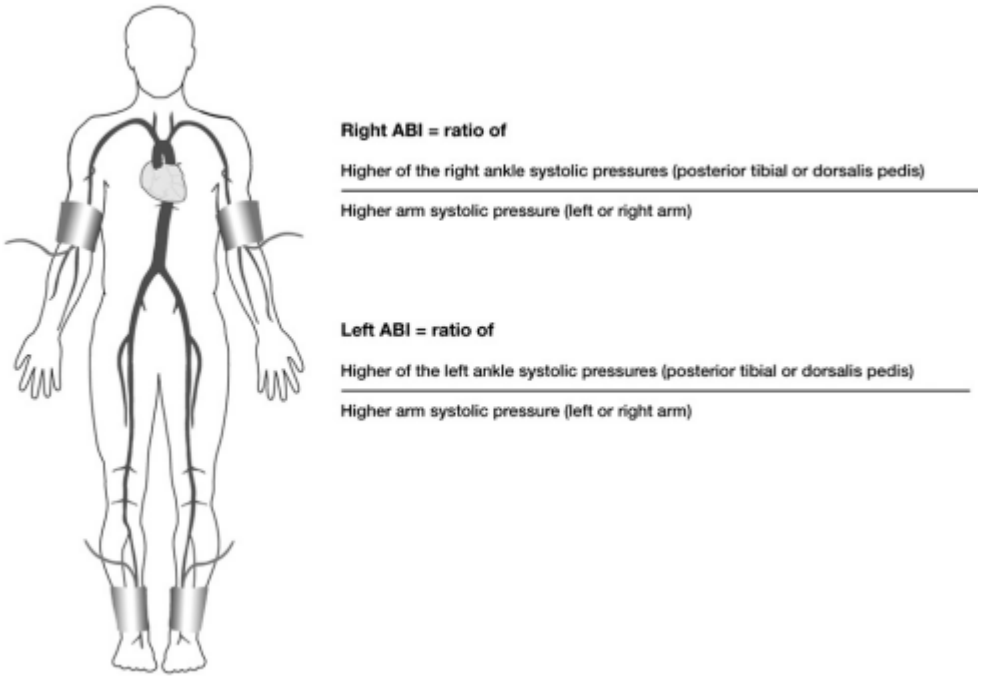

Figure 3: Measurement of the ABI. ABI – ankle-brachial index.

Exercise testing to establish the diagnosis of peripheral arterial disease

Claudication patients with an isolated isiac obstruction may not have a pressure drop across the obstruction at rest, resulting in a normal resting ABI, as previously mentioned. However, the increase in flow velocity that occurs with exercise would hemodynamically amplify such injuries. The reduction in ABI caused by exercise may be observed during the immediate post-exercise recovery phase, allowing doctors to diagnose PAD. The technique involves taking an ABI reading while the patient is at rest. Patients are then instructed to walk until claudication discomfort develops (or for no more than five minutes) on a treadmill while the ankle pressure is recorded (usually at 3.2 km/h (2 mph) and a 10%–12% gradient). PAD would be diagnosed by a drop in ABI of 15%–20%. If you don't have access to a treadmill, you may walk in the corridor or by climbing stairs.

Established Therapies for Management of the Systemic Atherothrombosis in PAD

Physicians caring for PAD patients may refer to a variety of guidelines for suggestions on the best ways to treat them. The American Heart Association and American College of Cardiology Foundation recommendations, as well as the worldwide Inter-Society Consensus (TASC) II guidelines, are examples of such guidelines. Both are currently receiving extensive revisions. Only 15% of the ACCF/AHA PAD recommendations, on the other hand, are based on data that is of a level A or above. The lack of high-level data limits the ability to make informed decisions.

Antiplatelet Therapy
Exercise Training
Statin Therapy
Carnitine and Propionyl-L-Carnitine Therapy
Pentoxifylline Therapy

4. Conclusion

There are many dermatological disorders for which pentoxifylline has been shown to be a safe and cost-effective treatment medication. As an adjuvant medication, it may be useful to dermatologists both as a stand-alone therapy and as an adjuvant to other treatment methods such as corticosteroids. There are a few studies that show pentoxifylline has beneficial benefits, but there isn't enough information to say if it has a role in other dermatological disorders. To be sure of its therapeutic efficacy, further research is required. Despite the scarcity of PAD-specific limb and systemic treatments, patients with PAD are at a very high risk of cardiovascular events and have a reduced quality of life as a result of rigorous treatment. Patients should be treated according to existing guidelines for other symptoms of atherosclerotic disease until further prospective, randomized studies are conducted in this group. There are currently just a few pharmaceutical treatments for treating claudication, such as cilostazol, and no additional medicinal methods to CLI that can be recommended.

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