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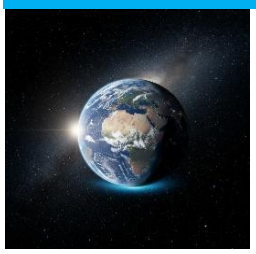

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Physical Activity and Other Strategies in Treatment of Buerger's Disease- a Systematic Review

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Abstract
Buerger's disease, also known as Thromboangitis obliterans (TAO), is a nonatherosclerotic vascular disorder of unknown etiology, causing distal arterial occlusions. Implication of changes in the vessels is decreased blood flow and ischemia as the result. Buerger’s disease is entirely associated with smoking. Diagnosis of TAO is challenging. Multiple diagnostic criteria have been suggested in the past years. Therefore it is advisable to base diagnosis on unified Delphi criteria. Patients suffering from TAO may present pain in digits as an early symptom, whereas late symptoms may include ulcers, gangrene and intermittent claudication.
Current management of TAO lacks standard guidelines. There is no one satisfying strategy, which can be implemented in every single patient. Various conservative and surgical methods might be performed. Each one has its own advantages and disadvantages. To this very day,

tobacco cessation is the cornerstone of the treatment. Important, although frequently neglected aspect is an exercise therapy. Modern, satisfying treatment methods are constantly explored.

Purpose

This study reviews currently available methods of treatment Buerger's disease to propose the most efficient way of treating this kind of disorder. We would like to give special attention to the role of physical activity in treatment of TAO.

Materials and Methods

A review of current literature was conducted, focusing on methods of treatment divided into two categories- conservative and surgical treatments. Advantages and disadvantages of mentioned methods were evaluated. Possibilities for the future were discussed. Literature available in the PubMed and Google Scholar databases was searched using keywords.

Results

Various methods of treatment may be performed. Each one has its own advantages and disadvantages. There is no gold standard for treating Buerger's disease. Individual approach and integrated care are the most important factors to provide satisfying management of the disease. Supervised exercise therapy has particular importance in ensuring acceptable quality of patient's life. Further studies are needed to improve effectiveness of treatment.

Keywords

Buerger's disease, Thromboangitis obliterans, Peripheral arterial disease, Ischemia, Treatment options

1. Introduction

Buerger's disease is a rare inflammatory disease of small and medium-sized arteries and veins, primarily involving distal extremities. This nonatherosclerotic disease affects all three layers of vessels in a segmental fashion [1]. It is well known that BD is strictly related to tobacco use. Although Buerger's disease mostly affects tobacco users, there is a subtype of TAO called "cannabis arteritis" which is related to marijuana smoking [2].

Typically, Buerger's disease develops in males between 20 and 50 years range. Women are affected significantly less often. They comprise 8% to 20% of patients in newest North American series. In recent years, a higher prevalence of TAO in women has been reported, due to the increase in cigarette smoking among women [3]. The vast majority of TAO patients are from lower-middle income socioeconomic class [4].

The cause of Thromboangitis obliterans is still unclear. Patients suffering from TAO do not have classical cardiovascular risk factors. Although, an association with endothelial dysfunction has been established [5]. It has been suggested that decreased fibrinolysis [6], enhanced coagulation activation [7] and tighter fibrin clots [8] may have significant role. The underlying cause of these changes is cellular infiltration, mainly in thrombus and intima, caused by inducible adhesion molecules (ICAM-1, VCAM-1 and E-selectin) and some inflammatory cells, such as CD4+ and CD8+ T-lymphocytes, CD 20+ B-lymphocytes, macrophages and S-100-positive dendritic cells. Elevated levels of pro- and anti-inflammatory cytokines and various autoantibodies (anti-endothelial antibodies, antibodies directed against vessel wall structures, anticardiolipin antibodies and antineutrophil cytoplasmic antibodies) have been also reported [9,10].

Course of the disease is progressive. TAO mostly affects upper and lower extremities. Patients typically seek medical attention due to pain in the fingers or toes. Patients might also develop reddish or purple discoloration, Raynaud's phenomenon, acrocyanosis or livedo-like pictures. In addition, clinical features such as ulcers, gangrene, phlegmonous and thrombophlebitic nodules are also common [11]. Symptoms may include intermittent claudication as well. As the disease progresses, patients may present non-erosive arthritis [12]. In rare cases, nail lesions can be the first sign of TAO. Chronic paronychia, proximal leukonychia or onycholysis and nail bed erosion may occur [13]. Patients suffering from TAO may also present ocular manifestations such as non-arteritic anterior ischemic optic neuropathy (NAION), occlusive retinal vasculitis and periphlebitis, papillophlebitis, central retinal artery occlusion (CRAO), branch retinal artery occlusion (BRAO), normal tension glaucoma (NTG), uveitis, chorioretinal atrophy, retinitis, papillitis, optic atrophy, changes typical for hypertensive retinopathy or abnormalities in electroretinography [14].

2. Diagnostic criteria

Due to difficulty in clinical assessment criteria based on Delphi study have been recommended. Diagnostic evaluation of Buerger's disease is now based on standardized clinical and angiomorphologic criteria. Patients can be divided into two categories- "definitive" or "suspected" Buerger's disease.

„Definitive" BD is confirmed if patient has history of tobacco smoking, typical angiography and typical pathology, all three at the same time [15]. It is specified that patient has to be current or past smoker, not second-hand smoker. The typical angiographic pattern includes smooth vessels without atherosclerotic plaque and lack of microaneurysm. Peculiar to TAO is Corkscrew collaterals, also known as Martorell's sign, distal arterial occlusion and skip lesions [15,16,17].

The term „suspected" BD might be used if patient has history of active tobacco smoking, which is a sine qua non condition and meets at least four other criteria- the disease onset at age less than 45 years, the ischemic involvement of the lower limbs, the ischemic involvement of any of the upper limbs, thrombophlebitis migrans or a red-blue shade of purple discoloration on edematous toes or fingers [15]. Thrombophlebitis migrans, known as Trousseau syndrome, is recurrent, sequential inflammation of the vein with an associated thrombus [18]. Ischemic involvement of the lower limb is defined as:

- absence of pulses of dorsalis pedis and tibialis posteriori of both limbs,
- ABI (ankle brachial index) <0.9 of both limbs,
- TBI (toe brachial index) <0.75 of both limbs, or
- signs of ischemia, such as skin atrophy, hair loss, nail thickness plus lack of any distal pulses of at least one limb.

Whereas, ischemic involvement of any of the upper limb can be confirmed if there is reported:

- positive Allen's test,
- Reynaud's phenomenon, or
- lack of radial pulse [15, 19].

Criteria for „definitive" BD diagnosis	
History of tobacco smoking	
Typical angiography	
Typical pathology	
Criteria for „suspected" BD diagnosis	
Major criteria	History of active tobacco smoking
Minor criteria	The disease onset at age less than 45 years
	The ischemic involvement of the lower limbs
	The ischemic involvement of any of the upper limbs
	Thrombophlebitis migrans
	A red-blue shade of purple discoloration on edematous toes or fingers

Table 1. „Definitve" BD is confirmed if the all three items available, whereas „suspected" is confirmed if patient has major criteria and at least four minor criteria [15].

3. Methods of treatment

Thromboangitis obliterans is a mutilating disorder, which significantly decreases quality of life. There is difficulty in increasing knowledge about rare diseases such as Buerger's disease due to a small number of large, randomized researches available. The unclear etiopathology is another huge obstacle to provide satisfying management of this disorder. Despite the fact that this disease affects a relatively small number of people, patients suffering from TAO definitely demand attention. Fortunately, over the last few years, a progress in methods of treatment has been made.

3.1 Conservative treatment

The most important therapeutic intervention is smoking cessation [11,20]. In the case of Buerger's disease every form of tobacco use is forbidden- including active smoking, passive exposure and substitution of smokeless tobacco [21]. Smoking is a crucial risk factor of initiation, maintenance, progression and treatment response of TAO. Without smoking cessation, every other method of treatment is insufficient to provide good quality of patient's life. Unfortunately, withdrawal form smoking is a demanding step for plenty of patients. TAO patients often require individual approach. Behavioral interventions and medication options, such as nicotine replacement therapy, bupropion, cytisine and varenicline should be considered [21]. In addition, TAO patients have to avoid vasoconstriction triggered by cold exposure or drugs to avoid impairment of blood supply to affected digits [22]. On the other hand, conservative treatment includes also pharmacological treatment. The outcome of pharmacological agents such as prostacyclin analogues (iloprost and clinprost), prostaglandin analogues (alprostadil), aspirin and folic acid has been evaluated in a recent Cochrane Review (Cacione, 2020) in individuals with Buerger's disease and critical limb ischemia. Relieving

pain, healing ischemic ulcers, amputation rates and ankle brachial index have been assessed. Moderate-quality evidence suggests that the intravenous iloprost is more effective than aspirin for eradicating rest pain and healing ischemic ulcers, although oral iloprost is not more effective than placebo. What's more, it has been reported that prostacyclin and prostaglandin analogues have not relevant difference for ulcer healing and relief of pain. Low-certainty evidence suggest that there is no clear difference in pain scores and amputation rates between folic acid and placebo, in people with TAO and hyperhomocysteinaemia. As was shown in Cochrane review, further efficacy assessment of pharmacological agents in TAO patients is urgently needed due to low-quality evidences [23]. Effectiveness of other medications, although widespread usage, have not been confirmed in large randomized trials. Single studies have reported that medical agents, such as vasodilators or cilostazol may improve pain-free walking distance but cannot prevent progression of the disease. Pentoxifylline used to belong to that group until recently. First case of patient, who achieved regression of Buerger's disease with pentoxifylline, has been described in 2025 [24].

3.2 Exercise therapy

Peripheral arterial disease (PAD) is a common disorder, which causes narrowing of arteries and decreased blood flow in lower limbs. The most frequent cause of PAD is atherosclerosis, induced by presence of fibrofatty plaques in intima of the vessel. These pathological lesions have multiple risk factors and are always associated with elevated level of low-density lipoprotein cholesterol (LDL) [25]. Other rare causes of peripheral arterial disease are, for instance, popliteal artery entrapment syndrome (PAES), cystic adventitial disease, fibromuscular dysplasia (FMD) or Takayasu disease. Obviously, at the bottom of PAD might also lay Buerger's disease. Common feature of each of these diseases is reduction of blood flow, especially to lower extremities. Thus, some methods of treatment, such as exercise therapy, might be performed in PAD caused by various causes. Treatment recommendations for PAD may not be directly applicable to patients with TAO [26]. What's more, the recommendations do not provide scale to assess effectiveness of exercise therapy on TAO patients. A root problem is lack of studies on patients suffering from Buerger's disease to evaluate effects of this method of treatment. Aim of physical activity in treatment of PAD is to develop collateral circulation. Such efforts provide angiogenesis in order to increase blood flow to lower extremities as therapy for leg ischemia [27]. Benefits of physical activity in PAD, such as improved walking tolerance, modified inflammatory/hemostatic markers, enhanced vasoresponsivness and adaptations within the limb that enhance oxygen delivery and metabolic responses have been described. Improvement of quality of life and extended longevity has been also reported [28]. Implementation of supervised exercise therapy (SET) for this purpose has been reported in recent case report (Komiya, 2023). Patient, despite smoking cessation, oral antiplatelet administration and angiogenic therapy, experienced exacerbation of symptoms eight years after diagnosis. SET has been performed once a week for forty minutes (including breaks) for five months. The exercise protocol involved the use of a treadmill with the speed and slope adjusted to induce leg pain within ten minutes. When pain appeared, treadmill was stopped and patient had to rest until the pain disappeared. When the walking distance extended the speed and slope were gradually increased. Additionally, patient was advised to perform home exercises by walking for at least 30 minutes, three times a week. Compliance to this advisement was not monitored. Results of this study were satisfying. Patient experienced improvement in initial and absolute claudication distance, even in five-month follow-up. Reduction in pain and subjective symptoms in the patient have been also reported. In conclusion, patient achieved improvement in quality of life. So far, use of physical activity in treatment of Buerger's disease wasn't evaluated in large clinical trials. Walking training plays an important part in treatment in PAD.

Further assessment of the role of physical activity in treatment this kind of disorder has to be studied. Possibilities of physical activity in treatment of TAO are promising [29].

3.3 Analgesia

A significant component of non-surgical treatment is pain management. Due to development of severe ischemic and neuropathic pain analgesia is crucial for patients suffering from TAO. Various methods can be performed, such as analgesics (often opioids in high doses are required), antidepressants, epidural anesthesia, neural block and local analgesia [11]. What's more, spinal cord stimulation has been evaluated in a few studies. It was reported that this method not only helps in pain management, but also improves microcirculation, especially in patients with ischemic lesions (ulcers and necrosis) of the lower limb [30,31]. However, there were some limitations in the applied search methodology- lack of control group and no reliable information about natural variation that occur in the TAO over time [30].

3.4 Endovascular treatment

Endovascular treatment plays a significant role in many peripheral vascular diseases. Unfortunately, interventional revascularization is impossible to perform in the majority of cases. Primary cause is that lesions in affected arteries are segmental, multiple and have distal localization. In addition, various advanced techniques, which are often available only in a tertiary care center, may be necessary to intervene to cross the lesion. Even if the lesion is passed, catheter-induced vasospasm can cause angiographically unsuccessful results [32].
Nevertheless, endovascular treatment should be considered as a therapeutic choice in patients suffering from Buerger's disease [33]. Series of endovascular procedures in Buerger's disease have been published with acceptable results in highly selected patients. In a recent study (Ghoneim, 2019) it has been reported that the endovascular management of Buerger's disease is safe and effective in conjunction with tobacco cessation. What's more, the procedure achieved high rate of clinical success, decreasing rates of amputations and maintenance of clinical improvement during a midterm follow-up period [33]. On the other hand, as was shown in other study (Serefli, 2022) the effectiveness of endovascular treatment declines significantly over time. The primary CLI-free rate at 12 and 24 months was 80%. Secondary CLI-free rates at 6, 12 and 24 months were 100, 93.3 and 53.3%, respectively. Patients who were active smokers during their follow up had a higher frequency of consultations [34]. The results of reports are promising, although further assessment is needed [32,35,36]

3.5 Open revascularization

Surgical treatment in patients with Buerger's disease is rarely possible as a therapeutic option [22]. In this method of treatment the most important question is if bypass is technically feasible [33]. The main obstacle is identifying a vessel, which can be used as a bypass graft. It is challenging, not only because of technical difficulties, but also due to pattern of involvement of vessels. Significant amount of vessels cannot be used, because they are completely occluded [37]. Other aspects, which should be taken into account to make decision about performing bypass, are life expectancy and complications caused by TAO [38]. In a systematic review (Salimi, 2022) it was reported that bypass surgery isn't more effective than smoking cessation or pharmaceutical therapy [39]. Nevertheless, open revascularization in patients with severe ischemia should be considered to provide better healing of ischemic lesions [40].

3.6 Sympathectomy

Sympathectomy is a procedure on the sympathetic nerves located in lumbar region (L2-L4). Aim of this procedure is to destroy sympathetic ganglion to widen the arteries, increase blood flow and consequently reduce pain. Sympathectomy can be performed by chemical neurolysis, radiofrequency or thermal ablation, or by various open surgical methods [41]. Unfortunately, there are low-quality evidences for the advantages of the sympathectomy. In the systematic review (Karanth, 2016) lack of randomized controlled trials assessing effects of lumbar sympathectomy has been described [42]. Although, improvements in pain relief and ulcer healing have been shown in newest study (Wei, 2025). A reduction in major amputation risk has not been reported. Compared with revascularization both strategies have similar amputation-free survival and cumulative wound healing rates. In addition, sympathectomy has additional advantages such as better pain management, lower Rutherford classifications, lower costs and shorter hospital stays [43]. Researchers are in complete agreement that further, large trials are needed.

3.7 Therapeutic angiogenesis

Aim of angiogenesis is to restore blood flow to ischemic tissue by artificially stimulating the regeneration and development of blood vessels [44]. New strategies for therapeutic angiogenesis, such as cell therapy and gene therapy, have been investigated as treatment options for Buerger's disease. For example, bone marrow-derived mononuclear, which contains endothelial progenitor cells but also angiogenic factors and cytokines, causes collateral vessel formation. It has been reported that therapeutic angiogenesis using bone marrow-derived mononuclear cells increases perfusion and consequently improves long-term amputation-free probability [45,46]. Recent studies confirm that another strategy, which is gene therapy with the application of vascular endothelial growth factor (VEGF) plasmid, is also safe and effective [47]. Moreover, these two methods might be performed simultaneously, which increase effectiveness of the therapy [48]. However, the number of studies and their participants isn't satisfying and further studies are needed. Surgical methods might also be performed to induce neovascularization. Intramedullary Kirschner wire technique or Ilizarov's technique of horizontal distraction can be promising [49,50]. What's more both methods are invasive and have peculiar complications, especially because they take place in ischemic area. On the other hand, new strategy of noninvasive treatment called LIPUS, has been reported. Low-intensity pulsed ultrasound (LIPUS) is effective and safe option, which induces angiogenesis. Until now, LIPUS was used to promote the healing of bone fractures in humans. This method also has some limitations- treatment group was relatively small and the optimal ultrasound parameters were unclear. In addition, evaluation of possible tardive adverse effects, such as cardiovascular outcomes and onset of malignancy weren't performed [51].

3.8 Immunoadsorption

Since assumptions of an immunopathogenesis of TAO are increasingly published, new methods of treatment are constantly explored. Immunoadsorption is widely used in immune-mediated diseases. Therefore, the implementation of this method of treatment seems to be promising. Immunoadsorption is a therapeutic apheresis technique that selectively removes immunoglobulins and circulating immuno-complexes from patient's plasma. Successful treatment of Thromboangitis obliterans with immunoadsorption has already been performed. Patients suffering from TAO achieved satisfying results as well as reduced pain, up to complete

lack of pain after one month, an increase in walking distance and improvement of healing ulcers [52]. Results of immunoadsorption have been also confirmed in other study (Klein-Weigl, 2012), where twelve patients were treated by immunoadsorption. Nine of patients noted improvement of ischemia, eight of them returned to work and a reduced intake of pain relievers was noted [53]. Another advantage of this method, despite of significant reduction of immunoglobulins, is low risk of side effects [54].

3.9 Bosentan

As previously mentioned endothelial dysfunction is the root cause of the Buerger's disease. Thus, treatment directed to improve endothelial function seems to be the right way. Bosnian is an oral dual endothelin receptor antagonist, primarily known for treating pulmonary arterial hypertension. In addition, bosentan is also used in the treatment of systemic sclerosis-related digital ulcers. As a result, the possibility of using bosentan in TAO began to be studied. In one of the research (De Haro, 2012) satisfying results of bosentan has been confirmed. Clinical improvement was observed in 12 of the 13 extremities, only two extremities underwent amputation after treatment and new ischemic lesions were noticed in only one patient [55]. Unfortunately, bosentan is not devoid of adverse effects. The most frequent side effects observed in patients, who are treated with bosentan are peripheral oedema, elevated liver enzymes, diarrhea, exacerbated dyspnea and nausea [56].

4. Conclusion

The management of diseases with low prevalence is certainly demanding. Development and implementation of accurate methods of treatment in Buerger's disease have faced also other challenges, as well as obstacles related to smoking cessation, low effectiveness of pharmaceuticals or technical difficulties of surgical treatment. Currently used strategies are inefficient to properly manage patients suffering from Buerger's disease. Thromboangitis obliterans is an important health issue as it mutilates especially young adults, causing constant pain, mobility problems, amputations and consequently disability. New methods of treatment are urgently needed. So far, the most important problem was unclear etiopathology. Recent studies are constantly improving our knowledge about an essence of the disease, which may eventually lead to the development of causal treatment. Meanwhile, individual approach provided by multi-disciplinary team has to be implemented.

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In preparing this work, the authors used ChatGPT for the purpose of searching for articles, summarizing articles, constructing sentences, enhancing english level. After using this tool/service, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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