



ORIGINAL RESEARCH PAPER

Surgery

CURRENT SCENARIOS IN MANAGEMENT OF BUERGER'S DISEASE AT TERTIARY HOSPITAL UTTARAKHAND

KEY WORDS: Buerger's disease, Thromboangiitis obliterans, Smoking, Gangrene, Amputation.

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ABSTRACT

Introduction / Background: Buerger's disease is a systemic vasculitis of unknown etiology, strongly associated with tobacco abuse worldwide. Buerger described Thromboangiitis obliterans (TAO) in 1908. High prevalence is found in Asian / Middle East countries. The survival rate of TAO is almost 90%. Presently, total abstinence from tobacco is the mainstay of treatment.

Aim: To determine the incidence, progression, etiology, impact of seasonal variations on admission, as well as, presentations, and treatment outcomes at our tertiary health care hospital in Uttarakhand region.

Materials: Patients of Buerger's disease admitted to our Institute during January 2015 to December 2019, were included in this study.

Methods: Retrospective analysis and study of 142 patients of Buerger's disease admitted at our institute.

Results: Most patients were males (97%), with mean age 38.6 years. The incidence & total TAO admission were overall decreasing during these years. Trends showed that eighty two (58%) patients were admitted between months of November to February (cold weather), while least in summers (15%). More than 50% were severe smokers (>30 bidi / cigarette per day). Pain in limbs was present in 77.4% cases. Major amputations were done in (12) 8% cases, while digital / finger / forefoot amputations in 31.69% / 3.52% / 10.58.% cases respectively. Lumbar sympathectomy was done in twelve cases. The median requirement of analgesic (opioids) by intravenous & oral route was 10 & 12 doses initially, & mean VAS score on day-1, 5 & 10 was 6.4, 4.1 & 2.9 respectively.

Conclusion: We conclude that incidence of TAO overall shows a decreasing trend, with better health practices. Admissions peak in the cold season, along with complaints related to painful / ulcerated limbs, with a strong association with tobacco abuse. Complete stopping of tobacco can halt further progression of TAO.

INTRODUCTION / REVIEW OF LITERATURE :

Buerger's disease or Thromboangiitis obliterans (TAO), is a non-atherosclerotic, segmental, inflammatory occlusive disease of small and medium sized arteries and veins, usually involving the extremities.¹ Besides limb vessels, TAO can also affect cerebrovascular, gastrointestinal & renal arteries as well.² Thrombosis & recanalisation of involved vessels may also be seen along with.

TAO usually affects young males commonly below 45 years of age, with the habit of tobacco use in any form. Initially, incidence was less than 1% in females, but an increasing prevalence among females has been reported in different countries.³ There was no difference in disease characteristics & prognosis between the male & female patients affected.⁴ The prevalence of Buerger's disease in peripheral arterial disease (PAD) patients varies as 0.5 to 5.6% in Western countries. The Indian subcontinent comes in the high prevalence region (45 to 63%),⁵ while Jews of Ashkenazi ancestry in Israel have ~80% prevalence. This variation may be due to variability in diagnostic criteria.⁶

TAO starts with ischaemia of distal small vessels of upper & lower limbs. Very rarely large arteries may also be affected without occlusive disease of small vessels.⁷ So, treatment of TAO is necessary as soon as possible, otherwise it may result in degraded quality of life, and social problems.

AIMS, MATERIAL & METHODS :

We aim to outline the epidemiology, progression, etiology, impact of seasonal variations, presentations and treatment outcomes, with follow up of cases of Buerger's disease at our

tertiary health care hospital in this hilly region of Uttarakhand.

Appropriate informed and written consent taken from patients included in this study. Appropriate documentation of all cases done and preserved. Appropriate Ethical Clearance sought from Institutional Ethical Committee / IRB. Google (Office Suite / Drive) (google.com/drive) used for data analysis, tabulation, manipulation, interpretation, graphing & charting, with results as observation numbers / percentages, statistical analyses and relevant comparisons. No conflict of interests; No source of support / funding. The content of this article was expressly written by the authors listed.

This retrospective study was carried out on all the patients with clinical diagnosis of Buerger's disease admitted under department of surgery at HNB Base Teaching Hospital & VCSGGMS&RI, Srinagar, Uttarakhand (India) during January-2015 to December-2019. A total number of 311 patients of PVD attended the institution, in OPD / Emergency. Of them, 142 patients of Buerger's disease required institutional indoor treatment.

Detailed history taking, including tobacco abuse & clinical examination including peripheral pulses, along with previous treatment modes & other relevant data regarding the admitted Buerger's disease patient in ward were recorded & collected. The Shionoya clinical criteria was used for diagnosis of Buerger's disease. It includes five criteria, which consists of (i)- Onset of disease before age of fifty years, (ii)- Presence of smoking history, (iii)- Absence of atherosclerotic risk factors, (iv)- Infrapopliteal arterial occlusions, (v)- Either upper limb involvements or phlebitis migrans.

All the patients were subjected to routine investigations, including X-rays of the involved limbs. Color Doppler ultrasound of both the involved extremities was performed to confirm the diagnosis of TAO. Arteriography of limbs was already done by some patients, with typical presence of collaterals & abrupt occlusion in distal extremities.

Exclusion criteria were atherosclerosis, hypertension, diabetes mellitus, ischaemic heart disease, arterial thrombosis due to trauma, hypercoagulable state, or collagen diseases such as Systemic lupus erythematosus (SLE) & Scleroderma.

Uncomplicated cases were managed by counseling and stopping abuse of tobacco in any form & continuing medical treatment till they become free from disease symptoms. For complicated cases (ulcer / gangrenous limbs) , a third generation cephalosporin antibiotic along with metronidazole & amikacin was infused intravenously till patients became afebrile in the perioperative period. In all cases of Buerger's disease, opioids (inj. Tramadol 50-100mg/dose) analgesics were used intravenously followed by oral analgesics after

admission. Pain was measured by VAS (visual analogue scale), with scores ranging from 0 to 10.

The patients were followed-up monthly for three months, followed by three monthly till one year after discharge from hospital. Patients having complications were admitted to the ward and managed accordingly.

RESULTS :

Out of one hundred forty two patients of Buerger's disease, 138 (97%) were males and only 4 (3%) females. The incidence of newly diagnosed TAO in each year in this five year duration (2015 to 2019) was 22 (84.6%) ,27 (81.8%) , 24 (80%) , 25 (89.2%) and 21 (84%) respectively. Already previously diagnosed and undergoing treatment cases of TAO were also admitted due to disease aggravation as follows : [2015; 4 (15.3%), 2016; 6 (18.1%), 2017; 6 (20%), 2018; 3 (10.7%), 2019; 4 (16%)]. Therefore, in 2015, total TAO patients admission was 26, while in upcoming years 2016, 2017, 2018 & 2019 were 33, 30, 28 & 25 respectively. They were in the age group between 20-56 years with mean age 38.6 years. Most of them were in the range of 26 to 50 years of age in both sexes. (Table-1).

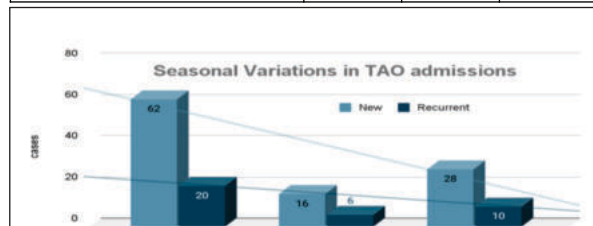
Table #1 : Demography / Epidemiology, Incidence, Progression (yearly; January 2015 To December 2019):

Year/ admission /sex	Newly diagnosed TAO	Already treated TAO	Total TAO patients admission	Male(M)			Total (M)	Female(F)			Both M+F	
				<25yrs	26-50yrs	>50yrs		<25yrs	26-50yrs	>50yrs		
2015	22(84.62%)	4(15.38%)	26	2	23	1	26	0	0	0	0	26
2016	27(81.82%)	6(18.18%)	33	3	26	3	32	0	0	1	1	33
2017	24(80%)	6(20%)	30	3	26	1	30	0	0	0	0	30
2018	25(89.28%)	3(10.72%)	28	2	21	4	27	0	1	0	1	28
2019	21(84%)	4(16%)	25	4	16	3	23	0	2	0	2	25
Overall	106	36	142	14	112	12	138	0	3	1	4	142
				138				4				

In this current study, it was observed that most of the TAO patients [82 (58%)] were admitted from November to February (cold season), of which 62 patients were new admission while 20 old (already treated TAO). It was also seen that about 15% TAO patients admission were in summers (March to June) while 27% in the rainy season (July to October) (Table-2).

Table #2 : Seasonal Variation:

S.No	Month	Season /weather	Total TAO patients admission	Newly diagnosed TAO patients	Already treated (known case TAO Patients)
1.	November - February	Winter (Cold weather)	82(57.74 %)	62(58.49 %)	20(55.55 %)
2.	March - June	Summer	22(15.49 %)	16(15.09 %)	6(16.66 %)
3.	July - October	Rainy	38(26.76 %)	28(26.41 %)	10(27.77 %)
Total			142	106	36



History of smoking was present in all the patients suffering from TAO. Some patients also had a history of use of tobacco in the form of quid & nicotine patches. In this study, about 35% of patients had a smoking history of 11 to 15 years duration,

while 28% had more than 20 years. In about 7% of patients, the duration of smoking was 1 to 5 years only. (Table-3). It was also observed that 51.4% patients were severe/heavy smokers (>30 bidi/cigarette/day) while 38% mild smokers (<20 bidi/cigarette/day) (Table-4).

Table #3 : Duration Of Smoking (years):

S.No.	Duration of smoking (Years)	No. of cases	Percentage(%)
1.	1-5years	10	7.04%
2.	6-10years	14	9.86%
3.	11-15 years	50	35.21%
4.	16-20 years	28	19.72%
5.	>20years	40	28.17%
Total		142	100

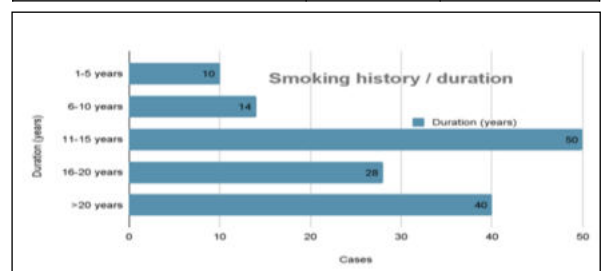
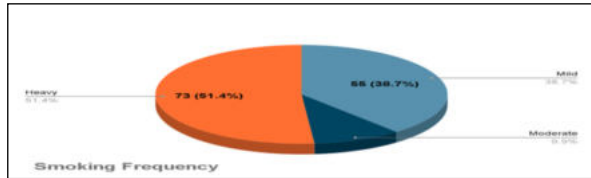


Table #4 : Frequency, Type & Number Of Bidi / Cigarette Smoking:

S.No	Frequency/Type of smoking	No. of Bidi/Cigarette /day	No. of TAO patients	Percentage(%)
1.	Mild	<20	55	38.74
2.	Moderate	21-30	14	9.86
3.	Severe(Heavy)	>30	73	51.40
Total			142	100



The main complaints of these patients were pain, gangrene, ulcer formation & color changes in limbs; alone or combinations of these. Pain with burning in limbs was present in more than 75% of patients while intermittent claudication (pain in lower limb on walking) in 65% cases. Rest pain was present only in 40% TAO patients on admission. Color changes in limbs were seen in about 26% of cases only.

Digital ulcer / gangrene was seen in about 63% cases while forefoot gangrene was frankly seen in 10.5% cases at the time of presentation in the hospital. Superficial phlebitis was also seen in 12 (8.4%) cases while upper limb complaints related to TAO was seen in about 7% cases. Anterior tibial artery (ATA) & Posterior tibial artery (PTA) pulsations were absent in 41.54% and 37.32% patients respectively. Ulnar artery (UA) pulsations were also absent in 13.38% cases overall.

We started treatment initially with use of analgesics (Opioids) by intravenous (IV) & oral route for pain control & assessment with use of VAS score. Antibiotic prophylaxis was also started to prevent infection either by oral or IV route in those TAO patients having ulcer or gangrene. Drugs like aspirin, clopidogrel (antiplatelet), pentoxifylline (hemorrhologic agents), calcium channel blockers (nifedipine), cilostazol (antiplatelet & vasodilator), isoxsuprine (vasodilator), atorvastatin (statins), antidepressant & steroids were used in different combinations along with absolute abstinence from use of tobacco.

In this present study, out of 142 TAO cases, 12 cases underwent major amputations (8%), while 45 (31.69%) for digital amputations. Disarticulation of digits / toes was also done in 10.56% cases. Finger amputations were done in 5 (3.52%) while hand amputation in 2 (1.49%) cases only. Forefoot amputations were done in 10.58% cases for gangrene. Redo amputations were done in at least 18.30% of cases also for further progression of gangrene proximally after first amputation. Lumbar sympathectomy was attempted in twelve cases with not much improvement in clinical symptoms.

Table #5 : Principal Complaints:

S.No.	Clinical features (Symptoms & Signs)	Number Of TAO Patients/ Total	Percentage (%)
1.	Pain & burning on feet / legs	110	77.46%
2.	Intermittent claudication	92	64.78%
3.	Rest pain	58	40.84%
4.	Color changes in limbs	37	26.05%
5.	Digital Ulcer / gangrene	90	63.38%
6.	Forefoot gangrene	15	10.58%
7.	Superficial phlebitis	12	8.45%
8.	Upper limb involvement/features	10	7.04%

DISCUSSION :

As the thromboangiitis obliterans (TAO) affects more of the young brigade of our society, it creates a huge economic burden as well as social morbidity to a family as well as to the growing nation. So, early diagnosis, disease prevention & aggressive treatment become essential to prevent further morbidity & mortality.

Males are usually affected more than females, as has been reported in ours as well as in most other studies. In our study, only 3% of patients were females, while in other recent studies, proportion of females affected with Buerger's

disease ranges between 11% & 23%.⁹ Only two female patients with smoking habits suffering from Buerger's disease have been reported by Njo KT & Smit AJ in 1996. Further, Buerger's disease incidence is increasing in women as shown in some studies (Yorukoglu Y, 1993).^{10,11}

In this study, the mean age of presentation was 38.6 years, while in a Japanese study 36.8 years was reported. Most of the patients were in the range of 26 to 50 years of age in our study, while in others, 20-65 years with mean age of 39 year has been reported.

In this study, incidence of TAO was more or less increased initially as in 2015 & 2016 as 22(84.6%) & 27(81.8%) cases respectively, but decreased in 2019 as 21(84%) cases. Similar pattern of admission in old treated cases of TAO due to disease aggravation was also seen. In a study done by Laohapensang K, between 1988 & 1995, at least 23 new, while 52 due to disease exacerbation cases of Buerger's disease were admitted, whereas between 1996 & 2002, the respective admission number dropped to 18 & 15 only. So there was a decrease in incidence of Buerger's disease in North Thailand also.¹² Matsushita M et al. also reported 46 & 12 new TAO admissions, while admissions due to disease exacerbation were 44 & 24 during study period 1985 to 1989 & 1990 to 1996 respectively.¹³ The new admissions as well as those due to disease aggravation appear to be more or less decreasing in number along with total TAO admission in our hospital.

Impact of seasonal variations on TAO admission was also seen in our study. We have seen that ~58% TAO patients were admitted in cold weather, while 15% in summer & 27% in the rainy season. A study conducted by Laohapensang K during 1987 to 2002, also reported the effect of seasonal variation on TAO admission. He reported at least 52% TAO admissions took place in cold while 11.6% during summer & 34.6% during rainy season.¹⁴ So more number of TAO patients were admitted in winter & less in summer. It is probably due to intense stimulation of vasospasm of medium & small size vessels of both limbs in cold weather while tendency of vasospasm is decreased (diminished) in warm weather.

In our study, more than one third TAO patients (35%) had the smoking history since 11 to 15 years while 28% for over 20 years duration. Mills JL (1987) & Shionoya S (1995) also observed the link between heavy smoking & Buerger's disease in their study.^{15,16} Starting smoking again after quitting smoking may also provoke the new flare up of the disease. So a firm relationship between smoking & pathogenesis of TAO has been established. In our study, most of the patients also had a history of use of tobacco in the form of quid, or nicotine patches. So smokeless tobacco may also contribute to the development of Buerger's disease.¹⁷ Smoking causes vasoconstriction, increased endothelial cell denudation & turnover. It also increases platelet aggregation & adhesiveness, with effects on coagulation, like increased blood viscosity & fibrinogen level.¹⁸ So all these contribute to limb ischaemia. This further establishes the role of smoking in progression of TAO.

TAO may be seen in non-smokers also, which possibly may be due to stimulating factors, such as frostbite, cold & abuse of sympathomimetic drugs.¹⁹ Cannabis abuse is also more common in India and may result in "cannabis arteritis". The clinical features of this are very similar to Buerger's disease but the reported differences in pathological lesions are not very convincing.²⁰

Lower limbs involvement or distal arterial involvement was more commonly present in this study. Proximal arterial involvement is rarely present. Thrombophlebitis was also seen in this study. It is usually of migratory type & runs parallel to arterial disease activity. There are no specific biomarkers for TAO.²¹ Inflammatory markers such as C-reactive protein

(CRP) are usually not correlating with disease activity. Biopsy can be performed without endangering the limb or if an amputation is performed.

Since pain was present in at least three-fourths of patients as the initial complaint, which was usually ischemic or neuropathic pain of high intensity, pain relief was started first in this study. We have used opioid analgesics by intravenous as well as oral route after admission in this study. Pain was measured by VAS (visual analogue scale), a score of integrated numbers ranging from 0 to 10. The median requirement of analgesic by parenteral (I.V.) as well as oral route was 10 & 12 doses initially. It was observed that the mean value for pain assessment by VAS score on day-1, 5 & 10 was 6.4, 4.1 & 2.9 after admission overall.

Further, antiplatelet drugs (aspirin & clopidogrel) in Buerger's disease patients may helps in relief to some extent, despite no proven evidence for their wide usage.²² In this present study, we have used steroids (prednisolone), which played a role in decreasing inflammation around ulcer & also pain relief. But various other studies suggest there is no proven evidence for use of steroids (immunosuppressant) in TAO.²³

In this current study, more than fifty percent patients underwent minor amputations, while 8% major ones, probably due to very delayed presentations at the hospital in this circuitous mountain region. In a study conducted by Takashi Ohta²⁴, they reported out of 118 patients, 13 (11%) underwent for major lower limb amputation, 33 (28%) for foot / toe, 12 (10%) for finger & 1 (1%) for hand amputation, after the onset of the disease. Redo amputations were done in at least 18.30% of cases for treating further progression of gangrene proximally after the first amputation.

We have found some improvement after doing lumbar sympathectomy in 8% cases in view of healing of ischaemic ulcer in this study. But few studies suggest that surgical sympathectomy seems to be dependent on smoking cessation.²⁵

CONCLUSION :

Ultimately, here we conclude that incidence of TAO admission is more or less on a decreasing trend nowadays, along with total Buerger's disease admission during these years, with peak admission in cold followed by rainy weather. We have seen a strong association between tobacco abuse & disease progression. Nowadays, because incidence of smoking is increasing in females worldwide including India, we have also seen female TAO cases in this study. Increased number of amputations for gangrene may be due to delayed presentation. Presently there is no single particular treatment available with excellent results so far, but complete cessation of tobacco will definitely be a boon for almost all the sufferers of TAO.

Author Contributions :

Dr. SP, KA, NC, KPS were involved in the treatment and management of the cases. SP, KA were involved in the formulation of this study and writing / editing of this article, while NC designed the tables and charts.

Abbreviations

[Symbols: $\cong \approx \sim \square \pm \sum \circ \uparrow \equiv \leftrightarrow \rightarrow \Rightarrow \S \int \infty \sqrt{\Delta \pi}$]

- Ant. – Anterior
- ATA – Anterior tibial artery
- PVD – Peripheral Vascular Disease
- TAO – Thromboangiitis obliterans
- CRP – C-reactive protein (CE)
- CT – (Contrast Enhanced) Computed Tomography
- Post. – Posterior
- I.V. – Intravenous
- PTA – Posterior Tibial Artery
- VAS – Visual Analogue Scale

HPE – Histo-Pathological Examination
 Sex – M: Males; F: Females
 VCSGMS&RI – Veer Chandra Singh Garhwali Government Medical Sciences & Research Institute (UT)

REFERENCES

- [1]. Olin JW, Young JR, Graor RA, Ruschhaupt WF, Bartholomew JR, The changing clinical spectrum of Thromboangiitis obliterans (Buerger's disease). *Circulation* 1990;82:IV3-8.
- [2]. H. Yun, D. Kim, K. Lee, S. Lim, W.Hwang, S. Yun, et al., End stage renal disease caused by Thromboangiitis obliterans: a case report, *J. Med. Case Rep.* 9 (2015) 174.
- [3]. Hida N, Ohta T. Current status of patients with Buerger disease in Japan. *Ann Vasc Dis.* 2013;6(3):617-623.
- [4]. Sasaki S, Sakuma M, Kuniyama T, Yasuda K. Current trends in thromboangiitis obliterans (Buerger's disease) in women. *Am J Surg.* 1999;177(4):316-320.
- [5]. Arkkila PE. Thromboangiitis obliterans (Buerger's disease) *Orphanet J Rare Dis.* 2006;1:14.
- [6]. Cachovan M: Epidemiologic and geographisches verteilungsmuster der Thromboangiitis obliterans. In *Thromboangiitis obliterans Morbus Winiwarter* Edited by: Heidrich H. Stuttgart, Germany Georg Thieme; 1988:31-36.
- [7]. Shionoya S, Ban I, Nakata Y, Matsubara J, Hirani M, Kawai S: Involvement of the iliac artery in buerger's disease (pathogenesis and arterial reconstruction). *J cardiovascular Surg (Torino)* 1978, 19:69-76.
- [8]. Lau H, Cheng SW. Buerger's disease in Hong Kong: a review of 89 cases. *Aust N Z J Surg.* 1997 may;67(5):264-9.
- [9]. Dehaine- Bamberger N, Amar R, touboul C, Emmerich J, fiessinger JN, Maladie de Buerger. Aspects cliniques et pronostiques: 83 observations. *Presse Med* 1995;22:945-8.
- [10]. Njo KT, Smit AJ. Thromboangiitis obliterans (Buerger's disease) in 2 women. *Ned Tijdschr Geneesk.* 1996, 140(35):1770-2.
- [11]. Yorukoglu Y, Igit E, Zengin M, Nazliel K, Salman E, Yucel E. Thromboangiitis obliterans (Buerger's disease) in women (a reevaluation). *Angiol.* 1993;44(7):527-32.
- [12]. Laohapensang K, Rerkasem K, Kattipattanapong V. Decrease in the incidence of Buerger's disease recurrence in Northern Thailand. *Sug Today* 2005;36(12): 1060-5.
- [13]. Matsushita M, Nishikimi N, Sakurani T, Nimura Y. Decrease in prevalence of Buerger's disease in Japan. *Surgery* 1998 Sep; 124(3):498-502.
- [14]. Laohapensang K, Rerkasem K, Kattipattanapong V. Seasonal Variation of Buerger's disease in the North part of Thailand. *Eur Vasc Endovasc surg* 28, 418-420(2004).
- [15]. Mills JL, Taylor LM, Porter JM. Buerger's disease in the modern era. *Am J Surg* 1987;154:123-9.
- [16]. Shionoya S, Leu HJ, Lie JT. Buerger's disease (Thromboangiitis obliterans). In: Stehens WE, Lie JT. Eds. *Vascular pathology*. London: Chapman & Hall Medical, 1995:667-78.
- [17]. O'Dell JR, Linder J, Markin RS, Moore GF. Thromboangiitis obliterans (Buerger's disease) and smokeless tobacco. *Arthritis Rheum* 1987;30:1054-6.
- [18]. Simon JC, Liody MT, John MP. Non operative treatment of chronic lower limb ischaemia. In: *Current problems in Surgery*. Wells SA (ed), Jan 1991. pp 45-46.
- [19]. Hagen B, Lohse S. Clinical and radiological aspects of Buerger's disease. *Cardiovasc Intervent Radiol* 1984;7:283-93.
- [20]. Combemale P, Consort T, Denis-Thelis L, Estival JL, Dupin M, Kanitakis J. Cannabis arteritis. *Br J Dermatol* 2005;152:166-9.
- [21]. Dragon PT, Landry GJ. Buerger's disease. *Ann Vasc Surg.* 2012;26(6):871-880.
- [22]. Piazza G, Creager MA. Thromboangiitis obliterans. *Circulatio.* 2010; 121(16): 1858-1861.
- [23]. Gur'eva MS, Baranov AA, Bagrakova SV, Kurdiukov AA. Pul's-terapiia gliukokortikoidami I Tsiklofosamidom v lechenii obliteriruiushchego trombangiita [pulse-therapy with glucocorticoids and cyclophosphamide in the treatment of thromboangiitis obliterans]. *Klin Med (Mosk).* 2003;81(10):53-57. Russian.
- [24]. Takashi O, Hiroyuki I, Ikuo S, Hirohide I, Jun K, Tetsuya Y, Masao T, Noriyuki H. The clinical course of Buerger's disease. *Ann Vasc Dis* Vol. 1, No. 2; 2008; pp 85-90.
- [25]. N. Liew, L. Lee, N. Hanipah, T. Gee, M. Jabar, Pathogenesis & management of Buerger's disease, *Int. J. Low. Extrem. Wounds.* 14(13), (2015); 231-235.