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Original Article

Evaluation of Risk Factors in Individuals with Vascular Thrombosis at High Altitude

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ABSTRACT

Objective: To evaluate the risk factors for developing vascular thrombosis at high altitude.

Study Design: Prospective longitudinal study.

Place and Duration of Study: Combined Military Hospital, Skardu Pakistan, from Mar 2018 to Feb 2020.

Methodology: All individuals evacuated from high altitude with suspicion of vascular thrombosis were consecutively inducted and evaluated radiologically. Subjects diagnosed as VT were further categorized on basis of height of evacuation into high altitude, very high altitude and extremely high altitude categories.

Results: Out of 295 individuals evacuated from HA, 54(18.3%) were diagnosed as VT. All patients were males. Mean age was 31+5.3 years. Cerebral venous thrombosis was diagnosed in 19(35%) and was the most frequent followed by pulmonary embolism in 18(33%) and deep venous thrombosis in 14(26%) patients. Risk of VT increased with increase in altitude as 05(10%) cases were from high altitude, 18(33%) were from very high altitude and 31(57%) from extremely high altitude. VT was more frequent in smokers [36 cases (67%), $p<0.05$] and in cold weather (37 cases (69%), $p<0.05$). Duration of stay has significant inverse correlation with height of deployment (r= -0.592, $p< 0.001$). Significant difference was found in duration of stay ($p<0.001$), haemoglobin ($p=0.016$) and haematocrit ($p=0.012$) among different categories of high altitude.

Conclusion: Cases of vascular thrombosis increase with increasing altitude even in shorter period of stay. Increasing haemoglobin and haematocrit with increase in altitude, cold environmental temperature and smoking are important risk factors for development of VT.

Keywords: Altitude, Embolism, Haemoglobin, Haematocrit veinous thrombosis.

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INTRODUCTION

A height of more than 8000 feet is defined as high altitude (HA). Pattern of diseases at HA differs from that at low altitude. The most feared event at HA is increased risk of vascular thrombosis (VT)[1]. The VT may be in the form of cerebral venous thrombosis (CVT), limb deep venous thrombosis (DVT), pulmonary thromboembolism (PE) or limb artery thrombosis and it is the third most frequent Cardio-vascular disease in Western countries[2]. At HA, the risk of VT is about 30-fold. Though risk factors for VT include advanced age, trauma, immobilization, surgery, obesity, underlying malignancy, pregnancy, estrogenic drugs, hereditary thrombophilic disorders like Protein C and S, antithrombin-III deficiency, anti-phospholipid antibody syndrome and factor-V Leiden mutation, most of VT at HA occur in young patients and in those who don't have any risk factors for such events[3].

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Different mechanisms for VT at HA have been proposed so far but the exact pathophysiology is still not well understood. The main culprit at HA is considered to be hypoxia[4]. In hypoxic conditions tissue metabolism is compromised. Toxic radicals are produced which may cause tissue and cell death. Another metabolic change observed in body, due to hypoxia, is shift from oxidative metabolism to glycolysis to meet energy requirement of the body[5]. Hypoxia also increases the production of erythropoietin resulting in secondary polycythemia[6]. Moreover, it leads to alteration in platelets functions and impairment in platelet-endothelium interaction. Thus there is progressive initiation and augmentation of the coagulation process by increased platelet adhesiveness, red cell anisocytosis, polycythemia and systemic inflammation in relation to exposure to high altitude[7]. All these mechanisms make the individuals living at HA prone to VT. Different treatment modalities have been suggested for HA disease, the single most important intervention being early descent. A number of preventive measures have also been mentioned in the literature; the most important being proper acclimatization[8].

This study aims to determine the frequency of VT and its different types in our patients and evaluation of risk factors for VT like height, duration of stay and hematology profile in individuals ascending to HA.

METHODOLOGY

The prospective longitudinal study was carried out at the Combined Military Hospital, Skardu Pakistan, after approval by Ethical Review Committee of CMH Skardu (ERC certificate No: 2018/12/03).

Inclusion Criteria: Individuals aged 19 to 60 years and of either gender evacuated from HA with suspicion of VT were included.

Exclusion Criteria: Individuals with previous history of thromboembolic event, procoagulant disorder and presence of preexisting conditions that increases the risk of VT were excluded.

Sample size was calculated using estimated population proportion of 15.9% of VT at high altitude[9] which came out to be 295. Using non-probability consecutive sampling, data was collected from March 2018 to Feb 2020 in accordance with the ethical standards of Helsinki Declaration of 1975, as revised in 2000.

Ventricular tachycardia in form of pulmonary embolism, deep venous thrombosis or cerebral venous thrombosis was diagnosed on basis of characteristic features in CT pulmonary angiogram, Doppler ultra-sound and CT cerebral venogram respectively. Patients diagnosed with VT were subjected to detailed history, clinical examination and laboratory investi-gations including Hb, HCt and platelet count which were analyzed using Sysmex XP100 Hema-tology Analyzer. All the above mentioned information was recorded on a predesigned proforma. Height of living was divided into three categories i.e. high altitude (8000 to 13000 feet), very high altitude (13001 to 18000 feet) and extremely high altitude (more than 18000 feet).

All data including demographic and biochemical parameters was analyzed by Statistical Package for Social Sciences (SPSS) version 20. Results were reported as the Mean±standard deviation for continuous variables and as frequencies and per-centages for categorical variables. Pearson correlation coefficient "r" was calculated for height of living with duration of stay. One-way ANOVA was used for multiple comparisons to compare different variables (such as age, height of deployment, duration of stay, Hb, HCt, Plt,) with categories of high altitude. The p-value of ≤0.05 was taken to be statistically significant.

RESULTS

Two hundred and ninety-five individuals from HA were evaluated for VT during study period. 54(18.3%) patients were diagnosed with VT, all being males. Mean age was 31+5.3 years. 27(50%) patients were below 30 years of age, 25(46%) patients were in age group 31-40 years while 02(4%) were above 40 years of age. Out of 54 cases, 19(35%) patients were diagnosed with CVT and 18(33%) as PE, 14(26%) had DVT while 02(4%) patients had combined CVT and PE, and 01(2%) patient had DVT and PE (Figure-1). As shown in Table-I, 37 (69%) cases were reported in winter season (Oct-Mar) while 17(31%) cases were evacuated in summer (Apr-Sep).

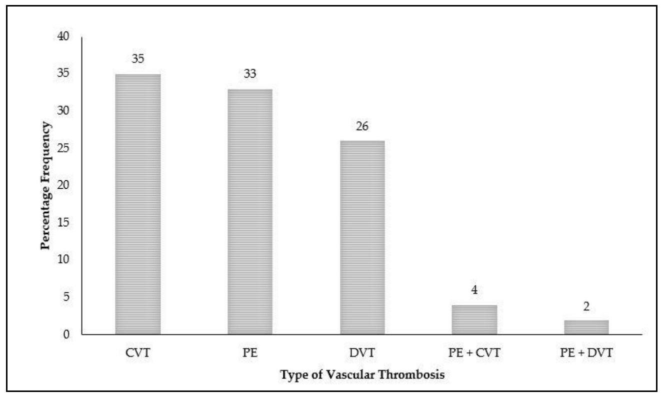

Figure-1: Percentage Frequency of various types of Vascular Thrombosis in sample population (n=54)

VT appeared to be more common among smokers as 36(67%) patients were smokers. There is statistically significant increase in number of VT cases (p<0.001) with increase in height of deployment as 05(09%) patients with VT were evacuated from height of 8000 to 13000 feet, 18(34%) from height of 13001 to 18000 feet and 31(57%) patients were evacuated from height of more than 18000 feet. A significant inverse correlation was also seen between duration of stay and height of deployment in subjects with VT (r=-0.592, p<0.001) as shown in Figure-2 and Table-II.

Comparison of various demographic and laboratory parameters among subjects with VT in different categories of high altitude shows significant difference in duration of stay (p<0.001), Hb (p= 0.016) and HCt (p=0.012) while no such difference is appreciated in mean platelet count (Table-III).

Table-I: Demographic, Clinical and Laboratory Features of Study Population Diagnosed with Veinous Thrombosis (n=54)

Characteristics	Mean+SD
Age (years)	31+5.3
Haemoglobin (g/dl)	16.6+2.2
Haematocrit (%)	47.9+6.2
Platelet Count (x 103/ul)	245+76
Smoking Yes No	n(%) 36(67) 18(33)
Season (Month) Winter (Oct-Mar) Summer (Apr- Sep)	37(69) 17(31)
Height of Deployment (Ft) High altitude (8000-13000) Very high altitude (8001-18000) Extremely high altitude (> 18000)	05(09) 18(34) 31(57)
Duration of Stay at High Altitude (Days) <30 31-60 > 60	18(33) 09(17) 27(50)
Diagnosis Cerebral Venous Thrombosis (CVT) Pulmonary Embolism (PE) Deep Venous Thrombosis (DVT) CVT & PE DVT & PE	19(35) 18(33) 14(26) 02(4) 01(2)

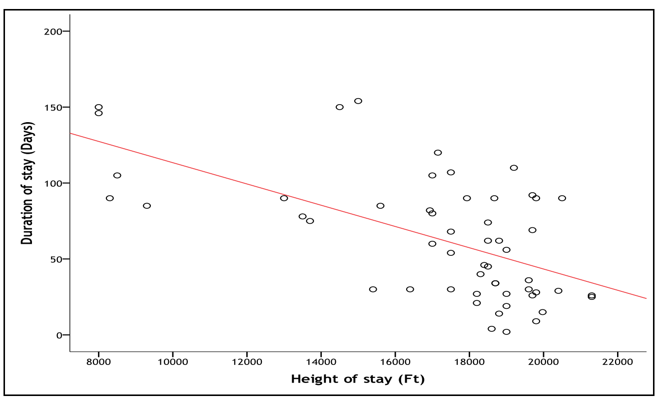

Figure-2: Scatter plot showing inverse relationship between height of stay (Ft) and duration of stay (Days) in patients having Veinous Thrombosis at High Altitude (n=54)

Table-II: Correlation between Duration of Stay at High Altitude and Development of Veinous Thrombosis (n=54)

Factors	Pearson Correlation Coefficient (r)	*p*-value
Duration of stay (days)	0.592	<0.001

DISCUSSION

Veinous Thrombosis confers significant cardiovascular morbidity and, in serious cases, death. There is 30 times higher risk of VT at HA especially in those living above 18000 ft[9]. However very few studies have been published so far on VT related to HA and no study has yet evaluated VT and its risk factors in different categories of HA. VT at HA has complex and poorly understood pathophysiology with interplay of genetic, acquired, and environmental risk factors[10]. Individuals ascending to HA are exposed to severe environmental stresses such as cold temperature, low humidity, increased ultraviolet radiation, decreased atmospheric pressure and low oxygen tension (hypoxia)[11]. Thus human body experiences various physiological adaptive changes for better adjustment to these environmental stresses like shift of oxygen haemoglobin dissociation curve, hemoconcentration and venous stasis, resulting in increased risk of thrombotic disorders[12]. Various studies have revealed that compensatory increased red blood cell and hemoconcentration at HA can cause activation of the coagulation cascade that later on progresses into a hyperfibrinogenic state and platelet dysfunction [13]. Some studies have shown that at high altitude of above 3500 meters, numerous factors including erythrocytosis, thrombocytosis, hyperfibrinogenemia and increased platelet activation along with hypoxia and dehydration create a prothrombotic state causing increased rates of VT in otherwise healthy individuals[14].

Table-III: Comparison of Various Demographic and Laboratory Features Among Subjects with Vascular Thrombosis Deployed in Various Categories of High Altitude (n=54)

Variables	Category I High altitude (8000-13000 ft)	Category II Very high altitude (13001-18000 ft)	Category III Extremely high altitude (>18000 ft)	*p* value
Cases of VT	n(%)	n(%)	n(%)	
	05(10)	18(33)	31(57)	
DVT	02(4)	05(9)	07(13)	
PE	02(4)	05(9)	11(21)	
CVT	01(2)	06(11)	12(22)	
PE + CVT	-	01(2)	01(2)	
PE + DVT	-	01(2)	-	
Duration of stay (days)	Mean±SD	Mean±SD	Mean±SD	
	115±31	83±36	43±29	<0.001
Haemoglobin (gm/dl)	14.1±1.9	16.8±2.3	16.9±1.8	0.016
Haematocrit (%)	41.2±4.3	46.4±5.8	49.8±5.8	0.005
Platelet (x 103/ul)	271±88	236±76	245±76	0.668

Our finding of CVT as commonest VT event followed by PE and DVT was also confirmed by another local study.[15]. However, one study reported DVT as most frequent type of VT followed by CVT and PE in Indian soldiers deployed at HA9. Our study has revealed that altitude has direct bearing on incidence of VT with majority cases occurring above

18000 feet. Smallman *et al*. has also indicated in his comparative study about incidence of thromboembolic events in U.S. Air Force Academy (at 7250 ft) with the U.S. Naval Academy and U.S. Military Academy (at sea level) that incidence of thromboembolic events was significantly greater even at moderate altitude[16]. About two-thirds of the cases of VT in our study population were smokers and were reported during winter season showing plausible role of smoking and cold temperature in pathogenesis of VT.

Our study has shown increase in frequency of all types of VT i.e. CVT, PE and DVT with increasing altitude contrary to another local study in which incidence of DVT was not affected by increase in altitude[15]. Increased frequency of DVT was contributed by restricted mobility and limited living space in addition to more intense weather conditions with increasing altitude. Moreover, several studies have reported hypoxia as independent risk factor for DVT at HA12-14,17. Our study also showed that 64% of DVT cases affected the left leg and more cases were of distal DVT than proximal DVT (93% vs 07%) similar to the findings of an international study[4].

Evaluation of hematology profile in our study population has revealed that individuals deployed at higher altitudes had more hemoconcentration as evident by significantly higher mean Hb and mean HCt but there is no significant difference in mean platelet levels. One explanation for the insignificant difference in the platelet is that platelet count may have decreased because of adaptability to the high altitude condition with continuous exposure to increased altitude as presented by Vij in 200918. Agnelli *et al*. and Vij AG have revealed that exposure to HA, especially in absence of acclimatization has been associated with an initial rise in platelet count and platelet dysfunction resulting in a prothrombotic state. After few days to few weeks, as the body acclimatizes to prolonged hypoxia, there is hemo-concentration and normalization of raised clotting factors. However, prolonged stay at HA leads to thrombocytosis, increased platelet reactivity resulting in increased risk of VT [18,19]. A recent study by Prabharkar *et al*. has also validated prothrombotic nature of HA and highlighted the importance of screening various markers as probable preventive measure to control of VT at HA20. Rocke *et al*. has demonstrated evidence of increased platelet reactivity and increased clot strength in whole blood assays in healthy volunteers exposed to altitude hypoxia that may increase risk of VT at HA3. However, in this study, wide disparity in our patients' exposure and stay at high altitude may have led to varying degree of adaptation to HA condition and insignificant difference in the platelet count with increasing altitude.

LIMITATIONS OF STUDY

Limitations of our study were lack of onsite investigative facilities especially haematology, coagulation and thrombophilia profiles that has limited our ability to evaluate and define causal relationship of possible risk factors with development of VT at high altitude.

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CONCLUSION

This study concludes that cases of vascular thrombosis increase with increasing altitude. Individuals at higher altitude can develop VT even with shorter duration of stay. Increasing haemoglobin and haematocrit with increase in altitude, and smoking are important risk factors for development of VT.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

AL: Data acquisition, critical review, approval of the final version to be published.

QA & MZ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MQ & SAS: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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