HIGH ALTITUDE AND VENOUS THROMBOSIS: FREQUENCY AND RISK FACTORS

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ABSTRACT

Objective: To determine the effect of high altitude on frequency and risk factors of venous thrombosis in individuals ascending to high altitude

Study Design: Cross-sectional analytical study.

Place and Duration of Study: Armed Forces Bone Marrow Transplant Centre, Combined Military Hospital Skardu, from Apr 2015 to Aug 2018.

Methodology: High Altitude was taken as height equal to or more than 8000 feet. Polycythemia as hemoglobin >16.5 g/dl OR hematocrit >49%. Medical records of all patients evacuated from high altitude through Combined Military Hospital Skardu were analyzed retrospectively. A proforma was designed to include necessary variables.

Results: We evaluated medical records of 539 individuals and found frequency of 86 (15.9%) for venous thromboembolism (VTE) at high altitude. Cerebral venous sinus thrombosis (CVST) was most common thrombotic complication seen in 39 patients (46%). Majority of thrombotic episodes occurred at >18000 feet (likelihood ratio (LR) 5.99, *p*-value 0.009). Majority of thrombotic episodes 34 (39%) occurred within first 45 days of ascent to high altitude. Thrombosis was linked to smoking 47 (55%) (likelihood ratio 21.3 and *p*-value <0.001) and use of melted snow as a source of drinking water 56 (65%) (likelihood ratio 57.6 and *p*-value <0.001).

Conclusion: This study showed a very high frequency of thrombotic complications at high altitude. There is a need for a robust prospective study covering epidemiology, clinical information and diagnostics in order to develop appropriate standard operating procedures and guidelines for prevention of thrombosis at HA

Keywords: Embolism, Polycythemia, Thrombosis.

INTRODUCTION

Gilgit-Baltistan has unique distinction of having some of the highest peaks of the world[1]. Individuals at high altitude in this region face not only the dangers of the extreme adverse environment but also the threat of serious high altitude (HA) illnesses[2]

HA induced venous thromboembolism (VTE) is a serious complication that is not well understood and studied[3]. All three factors of Virchow's triad i.e. venous stasis, hypercoagulability, and vessel-wall injury, appear to be present at HA and are hypothesized to contribute in pathogenesis of this serious and potentially fatal complication[4]. Studies have documented a 30 fold increased risk of thrombosis in individuals deployed at high altitude[5].

Pathophysiology of thrombosis at HA appears to be complex. An interplay between several factors including hypo-baric hypoxia, dehydration, hemoconcentration and low temperature, all appear to contribute to increased risk of thrombosis. This study was carried out to find out frequency and attempt to identify risk factors for thrombosis in individuals at HA.

METHODOLOGY

This cross sectional analytical study was carried out at department of Hematology, Armed Forces Bone Marrow Transplant Centre and department of Medicine, Combined Military Hospital Skardu. As previously documented studies, annual incidence of deep vein thrombosis at high altitude was much higher (0.7/1000) than in lowland (0.028/1000)[11]. Minimum Sample size was calculated with WHO sample size calculator

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using confidence level of 95%, margin of error 5%. All patients referred from HA with suspected thromboembolism were included in the study. Inividuals with past history of polycythemia, cardiovascular and pulmonary disorders and history of other chronic disorders were excluded from the study. Data was collected from 539 individuals by consecutive sampling. The study was approved by the Institutes' ethics committee for research (IRB AFBMTC) 03/18, and was in accordance with the ethical standards of Helsinki Declaration of 1975, as revised in 2000.

High Altitude was taken as ≥8000 feet, very high altitude >13000-18000 feet and extremely high altitude >18000 feet above sea level respectively. Polycythemia was taken as hemoglobin >16.5 g/dl or hematocrit >49%, whichever was higher[6]. Diagnosis of thrombosis was based on the following:

Deep vein thrombosis (DVT): raised D-dimers with positive duplex ultrasound, venography.

Pulmonary thromboembolism (PTE): raised D-dimers, positive CT-pulmonary angiography and /or ventilation perfusion mismatch testing.

Cerebralvenous sinus thrombosis (CVST): Positive CT-venography and / or Magnetic resonance venography.

Portal/hepatic vein thrombosis: raised D-dimers, positive Doppler ultrasound abdomen, CT venography.

Medical record of all patients evacuated with venous thromboembolism from high altitude through CMH Skardu were identified. A proforma was designed and validated to record necessary variables including age, altitude of deployment above sea level, duration of stay at that altitude, smoking history, water source, clinical signs and symptoms necessitating evacuation, hemoglobin / hematocrit along with investigations to confirm diagnosis. Cases with incomplete medical information were excluded.

A similar proforma was designed and validated to collect base line information about control population consisting of age and altitude.

All data were analyzed using SPSS version 23. Mean ± SD was used for quantitative data. Chi-square and student t-test were used and likelihood ratio was derived from category tables. A *p*-value of ≤0.05 was taken to be statistically significant.

RESULTS

Medical records of 539 patients evacuated from HA from January 2017 to July 2019 were analyzed. A total of 86 patients (15.9%) with thrombotic complications were identified. Frequency of thrombotic complications was 86 (15.9%). All were male with mean age of 27 ± 6.23 years. Altitude of deployment at time of thrombotic episode ranged from 8000 to 21300 feet above sea levels with a median altitude of 18400 feet. Duration of stay at HA ranged from 3 to180 days with mean of 52 ± 21.2 days. Mean hemoglobin level was 17.1 ± 1.8 g/dl. A total of 62 (72%) patients had a serious VTE (sVTE)- 39 patients CVST and 23 patients pulmonary embolism (PE) while 24 patients had deep vein thrombosis (DVT) alone (fig-1).

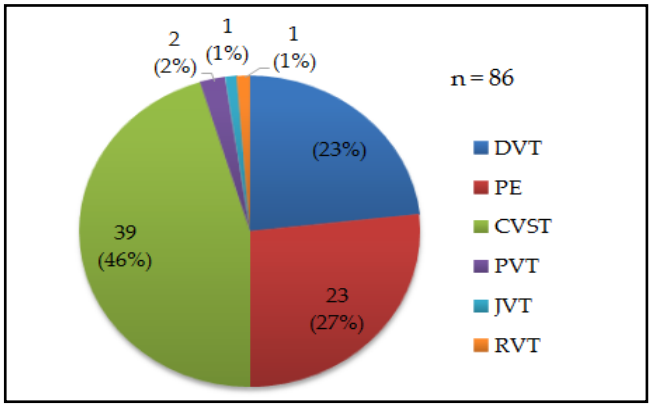

Figure-1: Frequency of thrombotic complications: CVST (cerebral venous sinus thrombosis), DVT (deep vein thrombosis), PE (pulmonary embolism), PVT (portal vein thrombosis), JVT (jugular vein thrombosis), RVT (renal vein thrombosis).

Majority of sVTE events occurred at extremely HA (>18000 feet), (likelihood ratio 5.99, *p*= 0.009) (fig-2) and within the first 45 days of ascent

to HA. Frequency of sVTE decreased with increasing duration of stay. On the other hand, frequency of DVT increased gradually with increasing duration of stay at HA, difference was statistically significant with p=0.01 (table). Thrombotic episodes were more common among smokers 47 (55%) (Likelihood ratio 21.3, p<0.001) and in patients using melted snow as a source of drinking water 56 (65%) (likelihood ratio 57.6 and p-value <0.001).

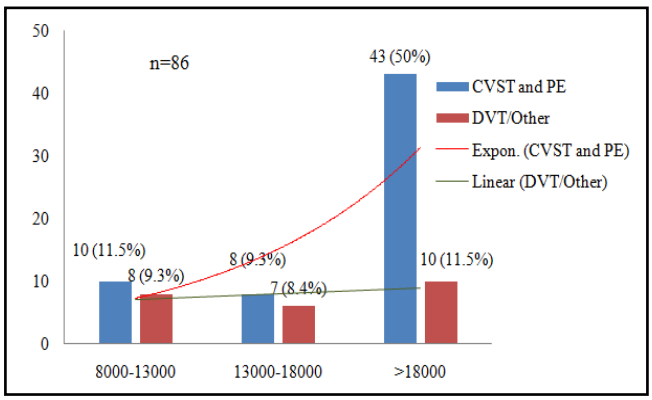

Figure-2: Relation of Altitude with thrombotic complications.

Table: Duration of stay and risk of venous thromboembolism: SVTE occurred early during stay at HA while frequency of DVT increased with increasing duration of stay (p=0.01).

Number of Days	CVST n (%)	PE n (%)	DVT n (%)
<45 days	19 (23.1)	12 (14.6)	3 (3.6)
45-90 days	11 (12.7)	5 (6.5)	8 (10)
>90 days	8 (9.7)	4 (5.5)	12 (14.5)
Column Totals	59	-	23

DISCUSSION

This study has three main findings. There was a very high frequency of thrombotic events at HA. sVTEs occurred mainly at extremely HA and occurred most frequently during early period after ascent to extremely HA; frequency appeared to decline with increasing duration of stay at HA. Incidence of DVT increased with increasing duration of stay at HA but was unaffected by increasing altitude.

A large number of case reports and small studies has been done on the subject of HA induced thrombosis but only limited data has documented these differences[7-9]. The above findings appear to point towards important differences in pathophysiology of sVTE and DVT. While DVT may be contributed by prolonged inactivity imposed by the weather and other environmental conditions, the factors underlying a predilection for sVTE at extremely HA remain elusive[10]. So far, the exact pathophysiological basis of HA induced thrombosis as a whole are poorly understood. Hypoxia and coagulation factor abnormalities leading to polycythemia and a hypercoagulable state have been long recognized[11]. Exposure to HA, especially in absence of acclimatization has been associated with an initial rise in platelet count, factor X, impaired clot retraction, shortening of prothrombin time and platelet dysfunction resulting in a prothrombotic state. Others have shown that increased D-dimer levels and activated protein-C resistance at high altitude contribute to hyper coagulability. After few days to few weeks, as the body acclimatizes to prolonged hypoxia, there is raised hemoglobin and hematocrit and clotting factor levels begin to normalize. Prolonged stay of more than 5 months results in thrombocytosis, increased platelet adhesiveness, increased factor VIII levels ultimately resulting in increased risk of venous thromboembolism (VTE), the risk continues as long as patient remains on the same height[12].

Approximately 12500 individuals were present at high altitude at any given time. Based on this figure annual incidence of thrombosis was 2/1000 compared to a reported incidence 1/1000 in the normal population[5]. These patients represented a selected cohort who were younger, fitter (with high activity level) and had lower incidence of VTE than the general population. A study from India demonstrated that those at HA were at 24.5 times increased risk of VTE than those serving in plains[12]. This study represented similar group of patients exposed to HA as in this study but frequency of Cerebral venous thrombosis was not mentioned in the study.

Cerebral venous sinus thrombosis is an unusual manifestation with incidence of 3-4 cases

per million in general population[13,14]. It remains a challenging diagnosis due to variety of clinical presentations and diagnosis is often delayed. However, CVST is frequently reported as a complication of HA exposure[15]. In this study frequency of CVST was 0.9-1/1000/year or 900-1000/million/year, approximately 66 fold higher than the general population. This increased propensity has been attributed to different factors at HA including dehydration, vomiting, polycythemia and hypercogulability[16]. However all these factors can lead to thrombosis elsewhere as well and it rem.ains unclear why there was predilection for CVST[17,18]. More studies involving emphasis on pathophysiological mechanisms is needed in this regard.

Altitude had direct bearing on incidence of sVTE with majority (63%) of events occurring at more than 18000 feet. Smallman *et al* compared incidence of thromboembolic events in U.S. Air Force Academy (USAFA) located at a 7250 feet with the U.S. Naval Academy (USNA) and U.S. Military Academy (USMA), both situated at sea level. Incidence of thromboembolic episodes were significantly greater for USAFA cadets indicating that even moderate altitude presents a risk factor for thromboembolic disease[19]. Exposure to HA also result in significant increase in hemoglobin levels, hematocrit, red blood cell count with consequent increase in blood viscosity and increased risk of thrombosis. Half of our patients had hemoglobin in the polycythemic range. However, hemoglobin and hematocrit of control population was not available and this would have been useful to establish any significant correlation.

In this study we found a strong correlation between smoking and thrombosis. Seventy five percent of evaluable cases in thrombosis group were smokers compared to 22% in control group and despite small number of evaluable patients in the thrombosis group, correlation was statistically significant with *p*-value <0.001 and likelihood ratio 21.6. This finding is of particular importance because relationship of smoking to HA associated thrombosis has not been documented earlier. Also, it is a modifiable risk factor.

The limitations of our study include small sample size, retrospective nature of analysis and lack of investigations to rule out heritable thrombophilia. Due to relatively small sample size, few risk factors may have been missed. As thrombophilia testing was not done, few patients may be having inherited thrombophilia with thrombosis provoked due to exposure to HA. The control group was not exactly matched in terms of the time frame in which data were collected.

CONCLUSION

This study documented a significantly higher likelihood of developing thrombosis at HA and points towards important differences in frequency and possibly pathophysiology of HA associated VTE at different sites. There is a need for robust prospective studies to further elucidate underlying mechanisms and allow formulation of preventive measures.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Joshi P. The battle for Siachen glacier: beyond just a bilateral dispute. Strategic Analysis. 2017; 41(5): 496-509.
2. Luks AM, Swenson ER, Bärtsch P. Acute high-altitude sickness. Eur Respiratory Rev 2017; 26(143): 96-98.
3. Singhal S, Bhattachar SA, Paliwal V, Malhotra VK, Addya K, Kotwal A. Pulmonary embolism in young natives of high altitude. Heart Views 2016; 17(2): 62-63.
4. Bärtsch P. How thrombogenic is hypoxia? J Am Med Assoc 2006; 295(19): 2297-99.
5. Anand AC, Jha SK, Saha A, Sharma V, Adya CM. Thrombosis as a complication of extended stay at high altitude. Natl Med J India 2001; 14(4): 197-201
6. Anand AC, Saha A, Seth AK, Chopra GS, Nair V, Sharma V. Symptomatic portal system thrombosis in soldiers due to extended stay at extreme high altitude. J Gastroenterol Hepatol 2005; 20(5): 777-83.
7. Chohan IS. Blood coagulation changes at high altitude. Def Sci J 1984; 34(4): 361-79.
8. Lee LH, Gallus A, Jindal R, Wang C, Wu CC. Incidence of venous thromboembolism in Asian populations: a systematic review. J Thromb Haemost 2017; 117(12): 2243-60.
9. Cancienne JM, Diduch DR, Werner BC. High altitude is an independent risk factor for postoperative symptomatic venous thromboembolism after knee arthroscopy: a matched case-control study of Medicare patients. Arthroscopy 2017; 33(2): 422-27.

10. McLaughlin CW, Skabelund AJ, George AD. Impact of high altitude on military operations. Curr Pulmonol Rep 2017; 6(2): 146-54.
11. Shishir K. High altitude induced deep venous thrombosis: a study of 28 cases. Indian J Surg 2006; 68(2): 84-88.
12. Agnelli G, Verso M. Epidemiology of cerebral vein and sinus thrombosis. Front Neurol Neurosci 2008; 23(2): 16-22.
13. Shrestha P, Basnyat B, Küpper T. Cerebral venous sinus thrombosis at high altitude. High Alt Med Biol 2012; 13(1): 60-62.
14. Devasagayam S, Wyatt B, Leyden J. Cerebral venous sinus thrombosis incidence is higher than previously thought: a retrospective population-based study. Stroke 2016; 47(9): 2180-82.
15. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. The incidence of cerebral venous thrombosis: a cross-sectional study. Stroke 2012; 43(12): 3375-77.
16. Zuurbier SM, Hiltunen S, Lindgren E. Cerebral venous thrombosis in older patients. Stroke 2018; 49(1): 197-200.
17. Duman T, Uluduz D, Midi I. A multicenter study of 1144 patients with cerebral venous thrombosis: the VENOST study. J Stroke Cerebrovasc Dis 2017; 26(8): 1848-57.
18. Smallman DP, McBratney CM, Olsen CH, Slogic. Quantification of the 5-year incidence of thromboembolic events in US. Air Force Academy cadets in comparison to the US. Naval and Military Academies. Mil Med 2011; 176(2): 209-13.