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HYPERCOAGULABILITY AT HIGH ALTITUDE:TO STUDY THE HYPERCOAGULABLE STATE AT HIGH ALTITUDE BY OBSERVING LEVELS OF COAGULATION PARAMETERS (D-DIMER) IN HEALTHY VOLUNTEERS

Medical Science

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ABSTRACT

High altitude areas exposes the human physiology to a myriad of challenges ranging from cardiovascular to respiratory to hematological and coagulation.In a prospective observational study conducted on 50 healthy volunteers inducting into high altitude(3000m) during their phase of acclimatization,blood samples were taken at day one and day six of induction into high altitude and the serial measurements analyzed to look for changes in level of DDimer.Significant changes in DDimer levels were noted ,moreso in volunteers with a higher BMI.

KEYWORDS

High altitude, hypercoagulobility, High Altitude Medicine, Coagulation, Hypoxia.

INTRODUCTION

Homo sapiens described by many as an epitome of evolution have progressed exponentially scientifically and have explored the planet to delve into its interaction with extremes of environments and terrains .Travel to high altitude areas exposes the human physiology to a myriad of challenges ranging from cardiovascular to respiratory to hematological and coagulation (1). High altitude is typically defined as heights ranging from 8000-1200 ft (stage one or high),12000-15000 ft (stage two or very high) and above 15000 ft (stage three or very very high). The atmosphere rarefies as altitude increases and the relative hypoxia induces a battery of adaptations in the body. The cardiac output increases consequent to changes in heart rate and blood pressure. Changes in respiratory system include increased alveolar ventilation , pulmonary hypertension and hypocapnia.Hematological changes include an increased hematocrit, raised platlet counts and activation and the combined changes of all systems contribute to a milieu favouring a state of hypercoagulability (2,3,4). This hypercoagulable state increases vulnerability to a gamut of pathological states ranging from deep vein thrombosis to strokes(5). With limited research on this aspect, there is a felt need to study the effects of high altitude on coagulation parameters.Fibrin degradation Products (FDP) and D Dimer are respectable markers of hyper coagulation and research into these markers would augment knowledge on this rare aspect(6).

AIM

To study the hypercoagulable state at high altitude by observing levels of coagulation parameters (D-Dimer) in healthy volunteers.

STUDY DESIGN

A Hospital based Prospective observational study.

LOCATION

A field hospital located at 3000 meters altitude.

SAMPLE SIZE

Similar studies on the subject have worked with sample size between 30-38.

The present study is aimed at a sample size of 50.

METHODOLOGY

The study was conducted on 50 healthy soldiers inducting into high altitude(3000m) during their phase of acclimatization. Blood samples were taken at day one , and day six of induction into high altitude and the serial measurements analyzed accordingly.

The following parameters were tested.

a) Hemoglobin (g/dl)
b) Haematocrit (%)
c) Red cell indices
d) Platelet count (×103/l)
e) D dimer

Inclusion criteria

a) Age 18-40 yrs.
b) Volunteer for the study.
c) Non smoker.
d) Absence of co-morbidities as hypertension, diabetes mellitus.

Exclusion criteria

a) Personnel not satisfying inclusion criteria.
b) Volunteers developing symptoms of Acute mountain sickness.
c) Personnel consuming alcohol or smoking during the study duration.
d) Personnel on or initiated on any medication .

Results

1. A total of 50 volunteers were selected for the study.
2. 42 volunteers could complete the study as the rest were not available for testing after 06 days.
3. Data was analyzed using SSPS software.

Descriptive Statistics

	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
D-Dimer day 1	42	.1667	.08165	.10	.40	.1000	.1000	.2000
D-Dimer day 6	42	.2143	.10493	.10	.40	.1000	.2000	.3000

Fig 1 Wilcoxon Signed Ranks Test

Ranks

		N	Mean Rank	Sum of Ranks
D-Dimer day 6 - D-Dimer day 1	Negative Ranks	8	6.81	54.50
	Positive Ranks	15	14.77	221.50
	Ties	19		
	Total	42		

Fig 2

Test Statistics

	D-Dimer day 6 - D-Dimer day 1
Z	-2.598
Asymp. Sig. (2-tailed)	.009**

BMI
Descriptive

BMI groups		N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
							25th	50th (Median)	75th
< 25	change DDimer	33	.0152	.10932	-.20	.30	-.0500	.0000	.0500
	BMI groups	33	1.00	.000	1	1	1.00	1.00	1.00
>=25	change DDimer	9	.1667	.10000	.00	.30	.1000	.2000	.2000
	BMI groups	9	2.00	.000	2	2	2.00	2.00	2.00

Fig 3 Mann-Whitney Test

Ranks				
	BMIgroups	N	Mean Rank	Sum of Ranks
change DDimer	< 25	33	18.56	612.50
	>=25	9	32.28	290.50
	Total	42		

Test Statistics	
	changeDDimer
Mann-Whitney U	51.500
Wilcoxon W	612.500
Z	-3.153
Asymp. Sig. (2-tailed)	.002**
Exact Sig. [2*(1-tailed Sig.)]	.002

Fig 4

4. The comparison of D-dimer results on day 1 and day 6 revealed an Asym 2 tailed result of 0.009 which is significant.The results were further analyzed to find co relation between BMI and D-dimer.

The data was divided into two groups BMI > 25 Kg/m2 and < 25Kg/m2 and change in D-dimer levels analyzed accordingly.There was a significant change in D-dimer levels in volunteers with higher BMI.

Disscussion

Barometric pressure reduces with increasing altitude varying in a non linear fashion as vertical height from the Earth's surface increases. Though the percentage of oxygen in the atmosphere remains static(20.9%),the atmospheric partial pressure of oxygen reduces proportionately.The atmospheric pressure is summation of constituent gases nitrogen, oxygen carbon dioxide , water vapour and others in trace amounts(2).

HYPOBARIC HYPOXIA

The ideal gas law defines the partial pressure of a particular gas in proportion to its percentage in a mixture. Thus the partial pressure of oxygen can be arrived at. P02 = Fi02 X Pb where PO2 is partial pressure of oxygen, FiO2 is fraction of oxygen in the atmosphere and Pb is the barometric pressure.Factoring for humidification which remains constant with altitude, the equation becomes

P02 = Fi02 X (Pb - P H2O) where P H2O is the saturated vapour pressure of water at body temperature.

Substituting the respective values at sea level
P02 = 20.9 % Fi02 X (101.3 kPa Pb - 6.3 P H2O)
P02 = 20.9 % X 95 kPa
P02 = 19.85 kPa

Now substituting the respective values at 5000 mtr
P02 = 20.9 % Fi02 X (56 kPa Pb - 6.3 P H2O)
P02 = 10.45 kPa

The above state of hypoxia translates down the oxygen cascade and reduces the oxygen availability to the mitochondria (2).

ACCLIMATIZATION-

The physiology of acclimatization includes multi system changes, particularly in the cardiovascular, respiratory and hematological system

CVS

An increase in cardiac output manifests primarily due to an increase in heart rate. The cardiac output is restored to sea level value in due time but heart rate remains elevated indicating a reduction in stroke volume.

RESPIRATORY SYSTEM

The hypoxic state induces hyperpnea to increase alveolar ventilation however, hypocapnia ensues. The respiratory alkalosis which results shifts the oxygen haemoglobin dissociation curve to the left thereby increasing haemoglobin affinity for oxygen but interference with oxygen release to tissue and mitochondrion also results.Over a few days an increase in 2,3- diphosphoglycerate shifts the curve to the right bringing the balance to its sea level position.

The hypoxic ventilatory response causes pulmonary hyperventilation to varying extent.

HEMATOLOGICAL CHANGES

Hypoxia stimulates erythropoietin leading to a rise in hematocrit and hemoglobin. Platelet counts also rise and also platelet adhesion contributing to a hypercoagulable state.

Inder Singh and S. Chohan in one of the earliest studies in the country on coagulation changes in high altitude followed up 38 serving personnel at altitudes between 12000-18000 ft. The study concluded an increase in Haematocrit , Platelet count, Plasma fibrinogen, Factor V , Factor VIII , fibrinolytic activity. While the aim of this particular study was to delve into the causes of pulmonary hypertension , it was concluded that the occlusive changes caused by the hypercoagulable state led to pulmonary hypertension(9).

Another observational study undertaken by Pichler-Hefti et al. investigated the effect of altitude on hemostatic parameters. Thirty four mountaineers, not high altitude residents, were randomly placed in two groups with different acclimatization schedules respectively. While the former climbed with a faster ascent and less acclimatization time (9 days acclimatizing at altitudes between 3750m- 5533m) the later group spent 13 days acclimatizing between 3750m – 5533m. Inclusion criteria were: previous trekking experience and experience withstay at high altitude. However persons with prior experience of Acute Mountain Sickness and or High Altitude Pulmonary Oedema were not excluded. Any evidence of cardiac or respiratory morbidity and regular administration of any medications formed exclusion criteria with the exception of analgesics (paracetamol, aspirin, ibuprofen, mefenaminic acid) as needed which were duly entered in a log book.

PT, activated partial thromboplastin time(aPTT), D-dimer, activated protein C resistance (APC-R), von Willebrand factor activity (RCo), ADAMTS-13 and C-Natriuretic Peptide (CNP) were tested . Acute mountain sickness was assessed using the Lake Louise AMS score.The study reported that D-dimer levels increased with altitude and so also PT leading to a procoagulant state. APC-R decreased and aPTT showed a significant increase. VonWillebrand factor RCo decreased. No significant changes were found in ADAMTS-13and CNP. The authors concluded that ascent to high altitudes activates coagulation and causes a procoagulatory state increasing succeptability to a thrombotic episode(4).

However, another prospective cohort study was performed in 2002 again on Indian soldiers deployed at high altitude by J Kotwal et al involving thirty eight soldiers who had normal physical exams before induction and no comorbidities or coagulation disorders at the start.They were followed up at induction , 03 months and 08 months. A similar group at sea level acted as controls,matched to the study group. Tests were conducted at 3500m. Thirty two soldiers could be followed for the full eight months.Hemoglobin, platelet count, fibrinogen, BTG, PF4, plasminogen activator inhibitor 1 (PAI-1), protein C, proteinS, antithrombin III, APC-R, Bleeding time (BT), Clotting time (CT), aPTT, PT and D dimer were studied.The authors reported an increase in hemoglobin, platelet count, fibrinogen, BTG,PF4, and PAI-1. No significant changes were found in protein C, protein S, BT, CT,APC-R, PT, aPTT and D-dimer. They also reported that the combination of increased hemoglobin from erythrocytosis, increased platelet count, increased fibrinogen , decreased fibrinolytic activity and increased PAI-1, causes an imbalance in hemostasis and increases risk of thrombotic events, however no significant changes were found in D-dimer level(7).

In our present study significant changes in D-dimer levels were observed during a six day acclimatization period,though long term follow up was neither intended nor carried out.In volunteers with BMI>25 ,changes in D-dimers were more as compared to the <25 BMI. However this aspect would require a seperate syudy with more number of participants.

In a study on 784 patients suspected of thrombosis between August 2003 and December 2004 found elevated D-Dimerlevels in patients of DVT , Cerebral thrombosis and DIC. They even arrived at a cut off value of D-dimer (7.87lg mL) which was the same for DVT and DIC. they concluded thatthat high levels of plasma fibrin-related markers reflect high risk for thrombosis(8). A review article by Soheir S. Adam

et al titled D-dimer antigen: current concepts and future prospects focuses on coagulation pathology and thereafter moving on to various methods to measureD-dimer with their relative sensitivitiy and specificity and finally concluding with various clinical applications of D-Dimer estimation. The article also pointed out that quantitative latex agglutination tests have excellent sensitivity and have been demonstrated to maintain good correlation with ELISA (10).

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