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Changes in Coagulation Factors at High Altitude: A Systematic Review

Abstract
Background: The numbers of individuals age 50 and over who maintain active lifestyles is growing. Many of these individuals travel to or live at, higher altitudes, to pursue outdoor activities or travel to higher altitudes for business. The use of anticoagulant therapy has continued to increase over the past two decades among individuals 50 and over. Warfarin is effective but requires a narrow therapeutic range based on the International Normalized Ratio (INR). Clinicians have concerns as to whether, ascending to higher altitudes, affects coagulation parameters and INR in warfarin patients.

Methods: A comprehensive search was conducted using Medline, CINAHL, Web of Science, Pubmed, and EBMR multifile. Three studies were chosen based on relevance to the topic. Each study was evaluated using GRADE criteria.

Results: Results from all three studies show that increase in altitude changes coagulation parameters indicating of a hypercoagulable state. A retrospective chart review determined that warfarin patients traveling to an altitude of 2400m had a significantly increased risk of subtherapeutic INR. An observational study on a high altitude expedition showed changes in coagulation parameters resulting in hypercoagulation. A cohort study of subjects ascending to high altitude also showed tendency towards a thrombotic state, especially an increase in fibrinolysis inhibitors, platelets and hemoglobin.

Conclusion: The studies show that altitude can change coagulation parameters which contribute to a hypercoagulable state and could decrease INRs of warfarinized patients in whom ascending to altitude increases the risk of thrombosis. The body of evidence was rated as low according to GRADE guidelines.

Keywords: Altitude, Coagulation, Anticoagulation, Warfarin, International Normalized Ratio (INR), Hypobaric, Hypoxia.

Degree Type
Capstone Project

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Changes in Coagulation Factors at High Altitude: A Systematic Review

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A course paper presented to the College of Health Professions

in partial fulfillment of the requirements of the degree of

Master of Science

Pacific University School of Physician Assistant Studies

February, 2011

Faculty Advisor: Torry Cobb, DHSc, MPH, PA-C

Clinical Graduate Project Instructors: Torry Cobb, DHSc, MPH, PA-C & Annjanette Sommers MS, PAC

Biography

[Redacted for privacy]

Acknowledgements

[Redacted for privacy]

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ABSTRACT

Background: The numbers of individuals age 50 and over who maintain active lifestyles is growing. Many of these individuals travel to or live at, higher altitudes, to pursue outdoor activities or travel to higher altitudes for business. The use of anticoagulant therapy has continued to increase over the past two decades among individuals 50 and over. Warfarin is effective but requires a narrow therapeutic range based on the International Normalized Ratio (INR). Clinicians have concerns as to whether, ascending to higher altitudes, affects coagulation parameters and INR in warfarin patients.

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INTRODUCTION

Background

In the United States, the expected population of individuals age 50 and older is estimated to rise to 100 million by 2012 (Pirkl, 2009). Baby Boomers (age 46-64) have continued to live an active lifestyle, refusing to settle for idleness. These individuals frequently travel all over the world pursuing outdoor recreation and adventure. Many travel to high elevations to visit national parks, ski in our nation's mountain resorts, and vacation in high mountain towns to golf, hike, bike and fish. A study in Nepal identified 20% of visitors applying for travel visas as 50 or older and one third of whom were planning to take part in mountain trekking (Shlim & Houstan, 1989). Some pursue more extreme activities throughout their 50s and later years, like high altitude mountaineering. The numbers of mountaineers over the age of 50 climbing Mt. McKinley (6194m) has increased since the National Park Service began standardizing expedition records in 1990 (McIntosh, Devitt, Rodway, Dow, & Grissom, 2010). The standard expedition route begins after a flight from sea level to base camp at 2190m. The number of climbers on Mt. Everest (8,848m), in 2000-2005, over the age of 59 quadrupled (Huey, Salisbury, Wang, & Mao, 2007). Not all of these Boomers or "Zoomers" have time for adventurous pursuits but many continue to work and travel for business to higher altitude locations (Pirkl, 2009). A large number live at higher altitudes in the U.S. and travel to lower elevations during the winter and return in the spring.

Ascent to higher altitudes causes hypobaric hypoxia and is known to cause physiologic changes in humans such as decreases in tissue oxygenation and

sympathetic compensatory changes; elevated systemic blood pressure; arrhythmias and vasoconstriction (Auerbach, 2007). Hyper viscous blood from hypobaric hypoxic altitude induced polycythemia could lead to a thrombotic state (Vij, 2009). There have been documented cases of healthy mountaineers suffering from altitude induced thrombosis and death (Bartsch, 2006). Pichler-Hefti et al. (2010), showed an increase in procoagulatory state with increased altitude. The increase in procoagulants has been seen without an equal counter response of fibrinolysis, thus creating a hypercoagulable state. The negative effects of high altitudes are worsened by comorbidities. Burtscher (2007) showed the risk of sudden cardiac death of hikers at altitude, increased significantly with history of prior myocardial infarction, diabetes, known coronary artery disease and hypercholesterolemia.

An increasing number of individuals 50 years and older remain active while successfully managing comorbidities such as hypertension, diabetes and hyperlipidemia. In addition to these conditions, some suffer from clotting disorders; history of deep venous thrombosis (DVT) or pulmonary embolus; atrial fibrillation (AF); valvular stenosis; history of stroke or transient ischemic attack (TIA); have a pacemaker; or have an artificial heart valve. These conditions usually require chronic, long-term or lifelong anticoagulant therapy to prevent either an initial or recurring thromboembolic event.

Warfarin, a vitamin K antagonist (VKA), has been successfully used for anticoagulant therapy for over forty years and is the most commonly prescribed VKA for long term anticoagulation (Fauci et al., 2008). Warfarin use has seen a threefold increase in the past two decades (Stafford & Singer, 1998). This is probably due to the

increase in treated AF. Warfarin, although effective, is at times difficult to manage due to the narrow therapeutic range. This range is defined by the International Normalized Ratio (INR). The typical therapeutic range for INR in patients being treated to prevent thrombosis is 2.0-3.0. The INR is a calculation that uses the prothrombin time (PT) blood test. Prothrombin time measures the clotting mechanism of the extrinsic coagulation system. The coaglulation cascade is dependent on coagulation factors produced in the liver and dependent on vitamin K formation. VKAs such as warfarin, delay the formation of vitamin K which prolong the PT. Significant changes in the INR (<2.0 or >3.0) can increase morbidity and mortality. The consequences of subtherapeutic anticoagulation include thrombus formation which can result in embolism and death. Supratherapeutic anticoagulation can result in hemorrhages that can also be life threatening. Hylek et al. (2003) found a 1.9 fold increased risk of stroke in AF patients with an INR of 1.9.

In addition to INR, clotting can be tested by measuring D-dimer, activated partial thromboplastin time (aPTT), activated protein C resistance (APC-R) and von Willebrand factor activity (RCo) in blood. D-dimer is produced by the action of plasmin on cross-linked fibrin. D-dimer is not produced when plasmin acts on fibrinogen not involved in clot formation. Thus, the presence of D-dimer confirms the activation of fibrinolysis, secondary to thrombin generation. Clot degradation can also be tested. One method is by measuring plasminogen activator inhibitor 1 (PAI-1), which decreases fibrinolysis. An increase in PAI-1 shows a decrease in breakdown of clot material leading to an imbalance in hemostasis. The intrinsic coagulation system can be tested with aPTT. Increases in APC-R show increased resistance to activated protein C which inactivates

procoagulant factors and increases risk for venous thromboembolic disease. Other tests examined by studies in this review are beta thromboglobin (BTG) and platelet factor 4 (PF4), which indicate platelet activation.

Purpose of the Study

The purpose of this paper is to perform a systematic review of the current literature regarding the affect of altitude on coagulation parameters. The results can then be applied to patients using warfarin therapy to prevent thromboembolic events when traveling to higher altitudes. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool will be used to evaluate the body of evidence (Guyatt, 2008).

METHODS

An extensive literature search was performed using PubMed, Medline, Web of Science, Cochrane Systematic Reviews, Evidence Based Medicine Reviews Multifile and CINHAL. These databases were accessed through the Pacific University Library system. The keywords searched were: Altitude, Coagulation, Anticoagulation, Warfarin, International Normalized Ratio, Hypobaric, Hypoxia, individually and in combination. The search was limited to human subjects. Articles published before 1989 were excluded. The initial search resulted in 24 articles. Subsequently, duplicate articles, traditional reviews and studies that focused on special populations other than warfarin patients and high altitude, were excluded. This resulted in ten studies, three of which were used in this review. The three studies used were chosen by the final inclusion criterion which was extended exposure to higher altitudes.

RESULTS

Risk of Impaired Coagulation in Warfarin Patients Ascending to Altitude (>2400m).

Tissot van Patot et al. (2006) investigated the factors associated with travel, to and from, altitudes that lead to a decrease or increase of INR values in patients using warfarin. The study was a retrospective review of medical charts of warfarin patients in a cardiology clinic located in Colorado at an altitude of 2400m. A total of 1139 INR measurements from 49 patients between August 1998 and October 2003 were used. Inclusion criteria for subjects were: current warfarin therapy and residency at the same location. The authors recorded the following chronic conditions or diseases: atrial fibrillation, hypertension, hyperlipidemia, valve replacement and cardiomyopathy. Travel was defined as descent from altitude and ascent back to home altitude. Low altitudes were between sea level and 1500m. When residents descended to lower altitudes, INR measurements were taken in clinics and results were faxed to the cardiology clinic. Travel period was defined as 60 days prior to travel (pre travel INR) and 14 days post travel (post travel INR). Inclusion criteria for INR measurements were: at least one travel associated INR measurement; up to five pretravel measurements per subject; initial post travel INR measurement. INR measurements were excluded if: pretravel measurement was taken less than 21 days after previous travel period; warfarin dosage was missed during travel period; warfarin dosage was changed during travel period; PT was considered unstable prior to travel period.

According to Tissot van Patot et al. (2006), warfarin patients without atrial fibrillation had a 2.7 fold risk of having a subtherapeutic INR after traveling to an altitude of 2400m (95% CI= 1.2-5.8); warfarin patients with atrial fibrillation had a 2.1 fold risk of

subtherapeutic INR at an altitude of 2400m (95% CI= 1.4-3.2); warfarin patients with atrial fibrillation and travel to an altitude of 2400m, had a 5.6 fold risk of subtherapeutic INR. The median reduction of INR with ascent to an altitude of 2400m after being at sea level for an extended amount of time, was -.56 (range= -1.3 to -.10) in patients with atrial fibrillation and -.70 (range= -1.7 to -.50) in patients without atrial fibrillation. The authors concluded that warfarin patients ascending to altitudes of 2400m or more, have an increased risk of subtherapeutic INR levels and should be subject to more closely monitored INRs.

Changes of Coagulation Parameters During High Altitude Expedition

A study conducted by Pichler-Hefti et al. (2010) was conducted from June 14-July 8, 2005 on Mount Muztagh Ata (7537m). This observational study investigated the effect of altitude on hemostatic parameters. Thirty four mountaineers, all lowland residents, were randomly placed in two groups. A different acclimatization schedule was given to each group. One group climbed with a faster ascent and less acclimatization time (9 days acclimatizing at altitudes between 3750m- 5533m). The second group spent 13 days acclimatizing between 3750m – 5533m. Base camp for both groups was at 4497m. All subjects spent two nights at 5533m, two nights at 6265m and one night at 6865m. Medical tests were performed at base camp and the three upper camps by 15 researchers who were not members of the subject groups.

Inclusion criteria were: previous trekking experience and experience with sojourns at altitude. Subjects with prior experience of severe acute mountain sickness (AMS) or high altitude pulmonary edema (HAPE) were not excluded. Exclusion criteria

were: evidence of cardiac or respiratory disease and regular use of medications. Subjects were allowed to use analgesics (paracetamol, aspirin, ibuprofen, mefenaminic acid) as needed. Medication use was entered in a log book. While these medications interfere with platelet function, Pichler-Hefti et al. (2010) reported, "We did not expect interaction of the medication used with the study results because endothelial and coagulation factor activation rather than platelet activation was the subject of our research" (Pichler-Hefti et al., p.112).

The hemostatic parameters tested were 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). Acute mountain sickness was assessed using the Lake Louise AMS score.

Pichler-Hefti et al. (2010) reported that D-dimer values gradually increased with altitude. PT increased with altitude indicating procoagulant changes and protein C inactivation. APC-R decreased and aPTT showed a significant increase. Von Willebrand factor RCo decreased. No significant changes were found in ADAMTS-13 and CNP. Secondary findings showed no relationship between AMS scores and coagulation parameters. Additional secondary findings showed a higher RCo and a lower ADAMTS-13 in the faster ascent group. The authors concluded that ascending to higher altitude activates coagulation and enhances procoagulatory state and could increase risk of a thrombotic episode.

High Altitude: A Hypercoagulable State: Results of a Prospective Cohort Study

A prospective cohort study was performed in 2002 on Indian soldiers deployed to high altitudes (Kotwal, 2007). Thirty eight subjects were randomly chosen to take part in the study. All subjects had normal physical exams before induction and no comorbidities or coagulation disorders were found. Tests were performed at enrollment, 3 months, and 8 months. Baseline studies were compared to a matched group who remained at low altitude. Tests were conducted at 3500m. Thirty two subjects were followed for the full eight months.

The inclusion criterion was: healthy soldiers age 20-40. The exclusion criteria were: comorbidities such as obesity, hypertension, and biochemical abnormalities. The following tests were done at enrollment, 3 months, and 8 months: hemoglobin, platelet count, fibrinogen, BTG, PF4, plasminogen activator inhibitor 1 (PAI-1), protein C, protein S, antithrombin III, APC-R, Bleeding time (BT), Clotting time (CT), aPTT, PT and D-dimer.

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. The authors reported that the combination of increased hemoglobin from erythrocytosis, increased platelet count, increased fibrinogen and increased PAI-1, causes an imbalance in hemostasis and increases risk of thrombotic events. Kotwal et al. (2007) concluded that extended stay at high altitude causes a hypercoagulable state.

DISCUSSION

The intent of this review was to examine the effect of ascending to higher elevations on coagulation factors. The initial literature search was directed at finding studies which evaluated the effects of long term increase in altitude on INR of warfarinized patients. Only one study was found which examined effect of increased altitude on INR of warfarinized patients. However, a substantial number of studies were found that focused on the effect of increased altitude on coagulation. A selected number of those studies were used in this review. Articles were chosen based on study of INR, extended stay of subjects at higher altitude, detailed description of methodology by the authors and high quality of the individual studies. Articles were excluded if they examined effect of altitude during airline flights or in laboratory built hypobaric chambers.

Grading the Evidence

Each common outcome in the studies reviewed was evaluated using GRADE. GRADE is a tool used to standardize the analysis and evaluate the quality of the data. GRADE ranks the evidence as very low, low, moderate or high (Guyatt et al., 2008). According to the GRADE Working Group, definitions of the GRADE ranks are as follows:

> High- further research is very unlikely to change confidence in the estimate of effect; Moderate- further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low- further research is very likely to have an important impact on our confidence in the

estimate of effect and is likely to change the estimate; Very low- any estimate of effect is very uncertain (Guyatt et al., 2008, p. 926).

All three outcomes used in this review had an initial rating of low based on a study design of observational. Only randomized controlled trials carry an initial rating of high, all other study types are given a low rating within the GRADE guidelines. Based on GRADE guidelines, an outcome grade can increase or decrease based on specific study parameters**.** Parameters that decrease high and moderate outcomes are study limitations, inconsistency, indirectness, imprecision and reporting bias (Guyatt et al., 2008). Parameters that can increase low or moderate quality of evidence are large magnitude of effect, dose-response relationship and control of confounders (Guyatt et al., 2008). The GRADE table examines the quality of evidence based on changes in coagulation parameters with an increase in altitude (Appendix, Table1). Each study showed a positive association with the outcome but the overall quality of evidence was rated low based on study design and absence of parameters that could have increased the GRADE rating.

Study Limitations

Several common limitations were present in each study. The first was small samples sizes. In the Tissot van Patot et al. (2006) study, there were 1139 INR measurements used, which is a significant number, but it came from 39 individuals. Even though these subjects were ideal candidates for the study, and for this systematic review, the study quality would have increased had they studied a larger population. The Pichler-Hefti et al. (2010) study had 34 subjects and suffered from the same

limitation. Overall, this observational study was executed with integrity and consistency. Likewise, the cohort study by Kotwal et al. (2006) suffered from the same limitation. Even though the results of these studies were statistically significant, larger sample sizes would have increased the GRADE rating. Replication of these studies with larger study groups would be difficult based on location.

Another common limitation of each study was failure to factor in diet as an effect on coagulation. It should be mentioned that during travel and mountain expeditions, an individual's intake of vitamin K can change due to a variation in diet. Deficiency in vitamin K can affect coagulation factors that are produced in the liver.

Two of the studies shared limitations that were not present in the third. The Pichler-Hefti et al. (2010) and Kotwal et al. (2006) used non-warfarinized subjects. Despite this, these studies were relevant to this systematic review due to their study of the effect of altitude on coagulation parameters. These studies were quality studies that showed altitude as a risk factor for hypercoagulation.

Another limitation of all three studies is that they failed to incorporate detailed data regarding the subjects' use of over the counter medications like aspirin and NSAIDS, which have anticoagulant properties. Even with this limitation, every study was able to demonstrate how altitude increases risk for hypercoagulation.

Conclusions

This systematic review reveals an increased risk of hypercoagulability at high altitudes. This hypercoagulability can have a negative effect on INR and therefore, an increase in altitude could increase the risk of a subtherapeutic INR. Clinicians who

have patients taking warfarin who are traveling to higher altitudes or clinicians working at higher altitudes whose warfarinized patients travel to lower elevations to escape the cold weather and return to higher altitudes with the warmer seasons may benefit from this review. It is suggested that clinicians caring for warfarinized patients, monitor INR more closely when their patients travel to higher altitudes. Furthermore, any patient using medications that may affect their coagulation parameters should be monitored more closely when spending time at higher altitudes.

There is not enough evidence or data to recommend a change of warfarin dosage in anticipation of a decrease in INR that could increase risk of thrombotic events. Future studies should be performed considering this clinical dilemma. Larger subject groups along with a greater number of INR measurements will yield better results. A range of increase in altitude could be examined to provide more precise changes in coagulation parameters, and length of stay at a variety of altitudes should be further investigated. Use of other interventions besides warfarin may become important. Future studies should also address diet and measure coagulation factors at baseline. Baseline should be described as being at home with a consistent diet.

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APPENDICES

Table 1. GRADE TABLE

Comparison	Outcome	Quantity and type of Evidence	Findings	Starting Grade	Decrease GRADE					Increase GRADE			GRADE of Evidence for Outcome	Overall GRADE of Evidence Base
					Study Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose-Response	Confounders		
	Changes in coagulation parameters with increase in altitude	3 observational studies	Positive Association	Low	0	0	0	0	0	0	0	0	Low	Low

Table 2. Kotwal et al. study results.

Table 2. Kotwal et al. study. Significant mean values of tests performed on subjects at induction to altitude; 3 months and 8 months at altitude.

TESTS	INDUCTION TO ALTITUDE	3 MONTHS AT ALTITUDE	8 MONTHS AT ALTITUDE
Hemoglobin	14.0	15.7	16.6
Platelet count	254	306	342
BTG	29.8	38.7	47.5
PF4	3.9	7.6	13.9
PAI-1	23.7	40.1	49.3
Fibrinogen	253	304	346

Table 3. Tissot van Patot et al. study results.

Table 3. Tissot van Patot et al. study. Increased risk of Subtherapeutic INR	
Risk Factor	*Odds Ratio with 95% CI*
Atrial Fibrillation	2.1
Ascent to Altitude	2.7
Ascent to Altitude with Atrial Fibrillation	5.6
Above values are compared to warfarin patient without atrial fibrillation and without ascent to altitude.	