NESTED CASE - CONTROL ANALYSIS OF THE RISK FACTORS FOR HIGH ALTITUDE PULMONARY OEDEMA

Lt Col RAJVIR BHALWAR*, Lt Col RANDHIR SINGH+,
Dr RC AHUJA#, RP MISRA**

ABSTRACT

A nested case-control study was undertaken on a cohort of soldiers inducted into high altitude area (11000 to 16000 feet) of Western Himalayas, with the objectives of studying the incidence of high altitude pulmonary oedema (HAPO) and its association with physical exertion and certain other predetermined risk factors. The study indicated that the cumulative incidence of HAPO was 1.42 per 1000 inductions. The association with moderate/strenuous physical exertion within 24 hours of entry into high altitude was significant (Odds ratio (OR) = 3.19; 95% confidence limits (CL) = 1.23 to 8.15); however, this association was not significant for the period 24 to 48 hours or > 48 hours. Physical exertion during first 24 hours was also significantly associated with severity of disease (OR = 14.67, 95% CL = 3.61 to 64.04), but not after 24 hours. Previous history of "high altitude sickness" was also significantly associated with HAPO (OR = 2.74, 95% CL = 1.12 to 6.77). Physical exertion during first 24 hours was found to carry an attributable risk of 2.56 per 1000 inductions and an etiologic fraction of 17.8%. No significant association of HAPO was observed with age, type of inductee (fresh/reinductee), native place, alcohol consumption and smoking.

MJAFI 1995; 51 : 189-193

KEY WORDS : Altitude; Pulmonary oedema; Nested case-control design; Risk factors.

Introduction

High altitude pulmonary oedema (HAPO) is a glaring example of man's fight against nature, not simply for his existence but rather to prove his dominance. The various clinico-epidemiological facets of this condition, particularly its prevention, are rapidly assuming importance, both for the medical world in general and the Armed Forces in particular. HAPO is easily one of the top priority issues in high altitude areas for commanders as well as for health functionaries because of the serious nature of the disease, the high fatality if not properly treated, the specialized nature of treatment and the shattering blow it deals to the morale of troops.

It was in the not too distant past when Houston in 1960 provided the first clear de-

scription of the condition in the English language [1]. This was followed by the pioneering studies by Menon [2] and Singh et al [3], on Indian troops, using the descriptive, case-series topology. However, there has been a conspicuous lack of analytic epidemiologic studies for generating incidence data and for providing information regarding the strength of association of certain putative risk factors with HAPO.

It was against the above backdrop that the present study was undertaken with the objectives of estimating the incidence of HAPO and to study the association of physical exertion with HAPO during the first 24 hours after entry into high altitude, while controlling for potential confounders like age, ethnicity, smoking and alcohol intake.

*Reader, Dept of PSM, AFMC, Pune 411 040. +Medical Specialist, Military Hospital, Alwar. #Professor of Medicine and Clinical Epidemiology; **Biostatistician; Clinical Epidemiology Unit, King George's Medical College, Lucknow.

Material and Methods

The present study was on the lines of a hybrid epidemiological design, using 'nested case-control' typology. The setting was that of a high altitude terrestrial environment, 11000 to 16000 feet above sea level, in Western Himalayas.

The study population consisted of an administratively and geographically clearly defined cohort of soldiers of a particular military formation inducted into the above area. All cases of HAPO in this cohort required compulsory admission to one particular hospital. Cases were not likely to be missed at the periphery because of strict and specific medical-administrative instructions. Thus, the entire well defined cohort could be followed till the onset of disease; all cases of the disease as they occurred in this cohort, could be tapped and could be compared with controls drawn from the same cohort. Hence the entire setting facilitated the present nested case-control design [4,5].

The outcome variable was HAPO, diagnosed by a physician, well experienced in high altitude medical practice, on the basis of clinical, radiological and ECG criteria, both for diagnosis as well as severity of HAPO. The exposure variable of primary interest was physical exertion within 72 hours of entry into high altitude. The exposure variables of secondary interest were age, native place, alcohol consumption, smoking, type of inductee (first time or reinductee) and previous history of high altitude sickness.

Sample size was calculated using an alpha (type I) error of 0.05 (two tailed), beta (type II) error of 0.20, expected proportion of cases with primary exposure variable as 26% ($p_1 = 0.26$), and among controls as 9% ($p_0 = 0.09$) and the power of study as 80%. The sample size required worked out to be 79 cases and controls each. The actual sample studied was 81 each of cases and controls. These 81 cases represented the total sample of all incident cases occurring in the cohort during one calendar year. There was no exclusion criteria; however, two fatal cases could not be

studied. There was no refusal or missing data point.

Controls were healthy, community based, drawn from the same parent cohort that gave rise to cases.

Frequency matching was done for location (thus controlling for altitude effect) and time of induction (within 15 days of the date of induction of cases) thus controlling for climatic effect. The exclusion criteria for controls was a history of severe acute mountain sickness (because such a control could have been mild, missed case of HAPO thus causing a differential misclassification bias). Three potential controls had to be excluded on this criteria. Controls were sampled once in two weeks, selecting an equal number of controls as the cases that had occurred during this period, by simple random sampling, from the complete list of defined cohort.

A questionnaire was developed based on the earlier studies, workers experience and expert advice. It was standardized in the population of interest to ensure construct, content and criterion validity. Certain dummy variables were inserted to enhance the test-retest validity. The questionnaire was used as a personal interview by the first author, who was blinded as regards case control status, to reduce observer bias. The codes regarding case/control status were handled by an assistant. Time taken to interview every tenth subject was noted to check any observer-induced - respondent's bias. Interviews were conducted within one week of recovery, to reduce recall bias. Subjects were assured of confidentiality and initial rapport was built up to reduce respondent bias. The physical exertion grades, which were standardized in the population of interest and used in this study are as below :

- a. Minimal : No activity expecting daily chores (meals, toilets etc.)
- b. Mild : Above + distance moved in a day < 1 km; distance moved in one stretch < 250 metres; No movement against gradient; No load carried;

- No feeling of dyspnoea.
- c. Moderate : Distance moved in a day 1 to 3 km; in one stretch 250-500 metres; gradient of climb < 30 degrees; load carried upto 5 kg; feeling of mild or moderate dyspnoea
- d. Strenuous : Distance > 3 km in a day; in one stretch > 500 metres; gradient > 30 degrees; load > 5 kg; feeling of marked dyspnoea

Presence of two or more criteria in a category qualified for physical exertion in that particular category of severity.

Grading of severity of HAPO was done on the basis of clinical, radiological and ECG criteria, taking into consideration the severity of dyspnoea, extent of lung involvement and evidence of pulmonary hypertension.

A pilot study was carried out on 10 cases and controls each. These pilot study subjects were included in the main study since certain changes were made in the schedule following pre-testing.

Results

Incidence : The study revealed a cumulative incidence (CI) of HAPO as 1.42 per 1000 inductions into high altitude, with a 95% confidence limit (95% CL) of 1.11 to 1.73 per 1000 inductions. The onset time (time gap between entry into high altitude and the onset of symptoms) had a median value of 54 hours with a range of 6 to 96 hours.

Association between HAPO and physical exertion : It was seen that physical exertion during the first 24 hours of entry into high altitude had a strong and significant association with HAPO (Table 1), the odds ratio (OR) being 3.19 (95% CL being 1.23 to 8.51). However, the association was not significant after 24 hours, the OR being 1.45 (95% CL being 0.65 to 3.23; $p > 0.05$) for 24 to 48 hours period. For more than 48 hours period, the OR was 0.82, with a 95% CL of 0.31 to 2.18 ($p > 0.05$). Thus, the main risk of developing HAPO due to physical exertion was during

TABLE 1

Association between physical exertion during first 24 hours and HAPO

Time period	Physical exertion grade	Cases	Controls
0 - 24 hrs	Moderate/strenuous	21	8
	Mild/minimal	60	73
	Total	81	81

OR = 3.19 (95% CL = 1.23 - 8.51); $p < 0.05$

the first 24 hours of entry into high altitude.

Association between severity of physical exertion and severity of disease : On a dichotomous scale, the study revealed a dose-response relationship, in that moderate/strenuous physical exertion during the first 24 hours had a strong and significant association with the severity of disease, the OR being 14.67 (95% CL = 3.61 to 64.04 (Table 2). On the other hand, after 24 hours, the association was not significant.

TABLE 2

Association between severity of physical exertion and severity of HAPO

Time period	Physical exertion grade	Severity of HAPO	
		Severe	Mild/moderate
0 - 24 hrs	Moderate/strenuous	12	9
	Mild/minimal	5	55
	Total	17	64

OR = 14.67(95% CL = 3.61 - 64.04); $p < 0.05$

> 24 hrs OR = 1.56 (95% CL = 0.44 - 5.60); $p > 0.05$

Association between previous history of high altitude sickness and HAPO : It was observed that a positive history of having suffered from acute mountain sickness during previous entries into high altitude had a significant association with the disease, the odds being almost three folds (Table 3).

Stratified analysis of the association between physical exertion and HAPO controlling for the confounding effect of "previous history of high altitude sickness : It was

TABLE 3

Previous history of high altitude sickness and HAPO

Previous history of high altitude sickness	Cases	Controls
Present	23	12
Absent	35	50
*Total	58	62

* - Analysis applicable only to 'reinductee' cases and controls; OR = 2.74 (95% CL = 1.12 - 6.77); $p < 0.05$

TABLE 4

Stratified analysis of the association between physical exertion and HAPO, controlling for previous history of high altitude sickness

Physical exertion grade	Previous history of high altitude sickness			
	Present		Absent	
	Cases	Controls	Cases	Controls
Moderate/strenuous	11	1	5	5
Mild/minimal	12	11	30	45
Total	23	12	35	50

Stratum OR 10.08 1.5
95% CL of OR 1.01 to 244.6 0.34 to 6.68

Fischer's exact p-value 0.03 0.73
(Significant) (Not significant)

Crude OR = 3.56; Mantel Haenszel OR = 2.9 (95% CL = 0.91 to 9.42)

Mantel Haenszel summary Chi-square = 3.06 ($p > 0.05$).
Woolf's test for multiplicative interaction : $p > 0.05$ (not significant)

observed that the association between physical exertion and HAPO was very strong and significant in those with a previous history of high altitude sickness, the OR being more than 10. On the other hand, this association was of a weak strength and not significant (OR = 1.5; $p > 0.05$) among those without such a history. After adjustment for this potential confounding effect, the Mantel-Haenszel adjusted OR came down to 2.9 as against the crude OR of 3.56. Although the adjusted OR was not significant (95% CL = 0.91 to 9.42; $p > 0.05$), this loss of significance was possibly due to a decline in the power of study, conse-

quent to low cell frequencies, as evident by the 95% CL of the adjusted estimate (0.91 to 9.42). The Woolf's test for statistically comparing the two stratum specific OR was not significant indicating that there was no effect - modification (multiplicative interaction) [5]. While subsequent studies using larger samples may further clarify this aspect, from the present study it can be concluded that a previous history of high altitude sickness seems to be an important determinant of HAPO and may accentuate the risk-effect of physical exertion.

Association between HAPO and other study variables : The other potential confounding variables, namely, age, ethnic group, inductee status, alcohol consumption and smoking were not significantly associated with HAPO (Table 5).

TABLE 5

Association of other study variables with HAPO

Study variables (cut-off criteria)	Statistical results
Age (≤ 30 vs > 30 years)	OR = 1.24 (95% CL = 0.62 - 2.46); $p > 0.05$
Native place (north/central/south India)	X = 2.21 df = 2; $p > 0.05$
Fresh/Re-inductee	OR = 1.29 (95% CL = 0.6 - 2.78); $p > 0.05$
Alcohol consumption (consumers vs non-consumers)	OR = 1.42 (95% CL = 0.64 - 3.18); $p > 0.05$
Tobacco smoking	OR = 1.36 (95% CL = 0.69 - 2.66); $p > 0.05$

Disease risk estimate for physical exertion : The present study being a nested case-control study, also allowed for the various risk estimates to be calculated for HAPO due to the exposure variable of primary interest (i.e. moderate/strenuous exertion during first 24 hours of entry into high altitude) [5]. It was observed that with a cumulative incidence of 1.42 per 1000 inductions and an OR of 3.19, the attributable risk is 2.56 per 1000 inductions (95% CL = 0.27 to 8.76) and the etiologic

fraction is 17.8% (95% CL = 2.22% to 42.59%).

Discussion

The overall incidence of 1.42 per 1000 exposures observed in the present study is somewhat lower than that reported by various other workers, viz. 3.4% by Hultgren et al [6] and 5.7 per 1000 air inductions by Menon [2]. The lower rate seen in the present study may be due to the better present day awareness of troops and commanders as regards preventive measures. Further, the present study did not notice any association of inductee status (fresh/re-inductee) which is in contrast with other workers who have reported a higher frequency among reinductees [2,7]. This may be because the earlier workers had counted the numbers but not compared the rates or proportions per reinductee or fresh inductee events. As regards 'induction time', the occurrence of a large majority of cases within 3 days of entry into high altitude has earlier also been reported by other workers [2,3,8]. Similarly, as regards smoking, no association was observed by Vishwanathan et al [9]. The observation that large number of cases undertook physical exertion soon after entry into high altitude corroborates well with other studies [2,3,7]; however no earlier study seems to have specifically studied this association according to different time periods in an analytic epidemiologic approach.

Based on the findings of this study it may

be concluded that avoidance of moderate or severe physical exertion specifically during the first 24 hours of entry into high altitude is crucial for prevention. With an etiologic fraction of 17.8%, such preventive measure is likely to reduce the incidence of HAPO by almost one fifth. In addition, special attention needs to be directed to those with past history of high altitude sickness.

REFERENCES

1. Houston CS. Acute pulmonary oedema of high altitude. *N Engl J Med* 1960; 263 : 478.
2. Menon ND. High altitude pulmonary oedema : A clinical study. *N Engl J Med* 1965; 273 : 66-73.
3. Singh I, Kapila CC, Khanna PK, Nanda RB, Rao BDP. High altitude pulmonary oedema. *Lancet* 1965; i : 229-34.
4. Klienbaum DG, Kupper LL, Morgenstern H. Epidemiologic research : Principles and quantitative methods. 1st ed. New York : Van Nostrand Reinhold Company, 1982; 67-152.
5. Schlesselman JJ. Case-control studies : design, conduct, analysis. 1st ed. London : Oxford University Press Inc., 1982, 69-104.
6. Hultgren HN, Spickard W, Hellreigel K, Houston CS. High altitude pulmonary oedema. *Medicine* 1961; 40 : 289-313.
7. Heath D, Williams DR. Man at high altitude : The pathophysiology of acclimatisation and adaptation. 2nd ed. Edinburgh : Churchill Livingstone, 1981; 72-181.
8. Kleiner JP, Nelson WP. High altitude pulmonary oedema - a rare disease? *JAMA* 1975; 234 : 491-5.
9. Vishwanathan R, Jain SK, Subramaniam S, et al. Pulmonary oedema of high altitude. *Am Rev Respir Dis* 1969; 100 : 334-41.