ORIGINAL RESEARCH

Nifedipine for the Treatment of High Altitude Pulmonary Edema

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Objective.—The purpose of this study was to assess the risk factors, patient profile, clinical features, and oral nifedipine as a treatment option for a series of 110 patients with high altitude pulmonary edema (HAPE) in a military hospital in India.

Methods.—This was a prospective cross-sectional study in a military hospital. In all, 110 patients with HAPE admitted and treated over a period of 3 years are reported. The following measurements were noted: dyspnea, cough, chest pain, cyanosis, pulse rate, blood pressure, respiratory rate, crepitations, radiographic abnormalities, electrocardiogram, peripheral pulse oximetry (SpO₂) at admission, SpO₂ normalization time, total leukocyte count, and length of hospital stay.

Results.—The risk factors identified for development of HAPE in our patients were improper acclimatization/faster rates of ascent, higher defined height (10 500 feet [3200 m]) for first stage acclimatization due to logistic reasons (usually 9000 feet [2743 m]), cold exposure, severe exercise, and respiratory infection. All patients were treated with reduction of altitude, supplemental oxygen therapy with nasal prongs, and bed rest. Oral nifedipine or placebo was administered to alternating patients. None of the patients deteriorated during their hospital stay, and all recovered fully to be discharged an average of 4.01 days (range 2–6 days) after admission. Patients were monitored for time taken for normalization of oxygen saturation, duration of hospital stay, time needed for resolution of lung crepitations, and radiographic infiltrates. Nifedipine administration was not found to be better than placebo for any of these variables ($P > .05$).

Conclusions.—Improper acclimatization remains the foremost risk factor for HAPE. In addition to descent and supplemental oxygen, nifedipine appears to provide no additional benefit in the resolution of HAPE.

Key words: high altitude pulmonary edema, nifedipine treatment option, high altitude illness

Introduction

High altitude pulmonary edema (HAPE) is a potentially fatal noncardiogenic form of pulmonary edema that can develop in unacclimatized persons usually within 2 to 4 days of rapid ascent to altitudes above 2000 m to 3000 m. The first descriptions of HAPE as a recognized form of noncardiogenic pulmonary edema were recorded in 1960 by Hultgren and Spickard¹ and by Houston.² Although HAPE can occur at as low as 1400 m,³ it usually occurs at higher than 3000 m. Indian army soldiers, by virtue of being deployed at heights of this magnitude, are at risk of high altitude illnesses. The incidence of HAPE among

Indian troops flown rapidly to 3500 m has been reported to be 15%.⁴ In addition to army personnel who are exposed to high altitude owing to their professional duties, mountaineering and recreational exposures also place participants at risk for these illnesses. Literature review on high altitude illnesses reveals a paucity of studies involving large series of HAPE patients. There are few randomized controlled trials evaluating different treatment strategies. Oxygen, rest, and descent are the common options available. Nifedipine has been recommended for patients who fail conservative measures or who have HAPE in remote locations where immediate descent is impossible.⁵

We designed a prospective trial to evaluate the efficacy of nifedipine for HAPE patients admitted and treated over a period of 3 years in our hospital.

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Table 1. Indian Armed Forces acclimatization procedure

First-stage acclimatization (6 days, 2700–3600 m)	
Activity	
Days 1 and 2:	rest except for short walks in the barracks only, no climbing involved
Days 3 and 4:	walk at slow pace for 1.5 km to 3 km, avoid steep climbs
Days 5 and 6:	walk up to 5 km and climb up to 300 m at a slow pace
Second-stage acclimatization (4 days, 3600–4500 m)	
Activity	
Days 1 and 2:	slow walk for a distance of 1.5 km to 3 km, avoid steep climbs
Day 3:	slow walk and climb up to 300 m
Day 4:	climb 300 m with equipment
Third-stage acclimatization (4 days, >4500 m)	
Activity	
	See second-stage acclimatization

Methods

During the study period (March 10, 2008, to December 31, 2010), 110 HAPE cases were admitted and treated in our hospital (1370 m). All were male soldiers serving in the Indian army. The established procedure for acclimatization in the Indian Armed Forces is described in Table 1; deviations were noted.

The diagnosis of HAPE was made based on Lake Louise criteria for HAPE; dyspnea, cough, tachypnea, crepitations, decreased oxygen saturation (SpO_2), and unilateral or bilateral pulmonary infiltrates on chest radiographs were noted. The clinical profile of all patients was noted and included age, gender, body weight, height, altitude at onset of symptoms, time gap between arrival at an altitude and onset of symptoms, and time from onset of symptoms to hospital admission. A record of the following variables was maintained: dyspnea, cough, chest pain, cyanosis, pulse rate, blood pressure, respiratory rate, crepitations, radiographic evidence, electrocardiogram, SpO_2 at admission to hospital, SpO_2 normalization time, total leukocyte count, and total hospital stay. Alternative diagnoses were ruled out with appropriate tests wherever required. All patients were treated with reduction of altitude, bed rest, nasal oxygen therapy ($4\text{--}6 \text{ L}\cdot\text{min}^{-1}$) and oral nifedipine (30 mg sustained-release tablet twice a day) or placebo. Nifedipine and placebo were alternated. Patients were treated until resolution of lung crepitations. The 2 groups were compared for time taken for normalization of oxygen saturation, resolution of lung crepitations, radiographic infiltrates, and duration of hospital stay. The Ethical Committee of the Military Hospital, Gangtok, duly approved the study.

Statistics

Mean and standard deviation were calculated using Microsoft software (Office Excel 2007, Microsoft Corp, Redmond, WA) for the outcome parameters in both groups. Unpaired *t* test was used to compare the difference in means between the 2 groups. A value of $P < .05$ was taken to be statistically significant.

Results

The clinical profile and clinical evaluation parameters of all patients are described in Tables 2 and 3.

Risk factors identified for the development of HAPE in our patients included improper acclimatization/faster rates of ascent (85 of 110 patients), deviation from the prescribed three-stage acclimatization schedule for ascent, and higher defined height (3200 m) for first-stage acclimatization because of logistic reasons. Cold exposure (2 of 110) and severe exercise (4 of 110) were considered precipitating factors as HAPE developed in these patients months after successful acclimatization. Severe exercise was defined as exertion that was intense enough to cause sweating, heavy breathing, or increased heart rate to near maximum. Respiratory infection was documented in a minority of patients (5/110).

Mean altitude at onset of symptoms was 3581 m (range 2286–4370 m). First symptoms started at a mean time of 56 hours after arrival at a particular altitude. Dyspnea was universal; cough was seen in 93.6% of patients at admission, although it was seen in all once resolution started. All patients had crepitations on auscultation (bilateral in 96.4%) and radiographic pulmonary infiltrates (unilateral in 29.1%). All patients had hypoxemia at the time of admission, and SpO_2 normal-

Table 2. Clinical profile of all patients (n = 110)

Characteristics	Data
Age (y)	31.3 ± 7.3 (20–47)
Male	110
Body weight (kg)	67.5 ± 6.1 (54–78)
Height (cm)	173.6 ± 2.9 (167–180)
Altitude at onset of symptoms (m)	3581.8 ± 483.1 (2286–4370.8)
Time from arrival at altitude to onset of symptoms (h)	56.00 ± 13.24^a
Onset of symptoms to hospital admission (h)	12.01 ± 3.73 (6–24)

Data are presented as % or mean $\pm$ SD (range) unless otherwise specified.

^a n = 104 patients (HAPE developed in 6 patients 2 to 3 months after successful acclimatization).

Table 3. Clinical evaluation parameters

Parameters	Data
Dyspnea	100
Cough	93.6
Chest pain	4.5
Cyanosis	9.1
Pulse rate (beats/min)	127.7 $\pm$ 6.51 (110–142)
Blood pressure (mm Hg)	
Systolic	128.7 $\pm$ 8.0 (110–150)
Diastolic	82.3 $\pm$ 4.5 (70–90)
Respiration rate (breaths/min)	28.4 $\pm$ 3.9 (18–40)
Crepitations	
Unilateral	3.7
Bilateral	96.3
Radiographic evidence	
Unilateral	29.1
Bilateral	70.9
Electrocardiogram	
Normal	93.7
Right ventricular strain	6.4
Spo ₂ at admission (%)	75.7 $\pm$ 4.4 (62–82)
Spo ₂ normalization time (h)	41.1 $\pm$ 8.4 (20–68)
Total leukocyte count (/mm ³)	11,235 (8500–13 900)
Total hospital stay (d)	4.0 $\pm$ 0.1 (2–6)

Data are presented as % or mean $\pm$ SD (range) unless otherwise specified.

ized in a mean time of 41 hours (20–68 hours). None of the patients had any evidence of infectious, cardiogenic, neurogenic, or toxic pulmonary edema. The mean leukocyte count was 11 235/mm³ (8500–13 900/mm³). Fifty-five patients had HAPE on first exposure to high altitude (initial exposure HAPE), and the remaining subjects had HAPE after a period of absence from high altitude (reexposure HAPE) while being on leave or on duty away from that altitude for a variable time. The minimum period of absence leading to HAPE on arrival back to high altitude was 10 days.

None of the patients showed any signs of deterioration during hospital stay, and all recovered fully to be discharged at a mean of 4.01 days (2–6 days) after admission.

Discussion

The most reliable management modality for HAPE is immediate descent (at least 500 to 1000 m) or supplemental oxygen, or both. If oxygen is not available and immediate descent is not possible, a portable hyperbaric chamber can simulate a descent of 1500 m or more and is a good temporizing measure before definite therapy in the form of descent can be offered.⁶ Pharmacological

therapy can be offered as an adjunct to these measures. Oelz et al^{5,7} demonstrated that nifedipine decreased systolic pulmonary artery pressure (by 50%), narrowed the alveolar-arterial oxygen gradient, and led to improving radiographic scores as pulmonary edema cleared, although without a significant improvement in arterial oxygenation. Hackett et al⁸ compared several vasodilators as treatment for HAPE and found that nifedipine (10 mg) reduced mean pulmonary artery pressure and pulmonary vascular resistance by approximately 30%, with improved oxygenation and slight decreases in mean arterial blood pressure.

Gabry et al³ reported a series of 52 patients at moderate altitude (<2400 m) and documented dyspnea (96%), moist rales (77%), cough (72%), cyanosis (59%), and chest pain (17%) in their patients. In our series, cyanosis (9.09%) and chest pain (4.54%) were relatively less. Six of our patients had HAPE at 2286 m. Persons with a history of HAPE appear to be more prone to recurrence, as described in North and South America.^{9,10} Factors previously reported to increase the risk of HAPE include a history of HAPE,¹¹ faster rates of ascent, higher altitudes, male gender,^{12,13} cold ambient temperatures,^{13,14} preexisting respiratory infection,¹⁵ and intense exercise.¹⁶ We documented 2 cases with extreme cold exposure and 4 cases with intense exercise leading to HAPE in otherwise well-acclimatized persons. Preexisting viral respiratory infection may be a documented risk factor for the development of HAPE, presumably due to alteration of vascular permeability by inflammatory mediators.¹⁵ We documented presumed precedent viral respiratory infection in only 5 patients. Preexisting cardiopulmonary disease, heavy exertion on arrival to altitude, low altitude residence before ascent, and obesity are risk factors, whereas youth and physical fitness do not seem to convey protection.¹⁷ Cold ambient temperatures and vigorous exercise contribute to an increase in sympathetic activity, which in turn contributes to the increased pulmonary artery pressure and pulmonary hypertension of HAPE.¹⁸ That may explain the development of HAPE in 6 of our patients, 2 cases due to cold exposure and 4 due to severe exercise. Nifedipine administration was not found to be superior to placebo for any of these variables.

Although nifedipine is the only well-studied drug in the treatment of HAPE,^{5,7} it is not clear that it speeds the resolution of HAPE when used along with oxygen and descent. Questions remain regarding the efficacy of nifedipine in the resolution of pulmonary edema, especially when it is being used along with oxygen support. Future HAPE research should be directed toward comparing the effectiveness of oxygen and nifedipine indi-

vidually. Currently, the modalities that consistently help HAPE are descent along with oxygen support.

Study Limitations

All subjects were male and, hence, the data may not be applicable to female patients. In addition, the option of descent was always available, and these results may not apply where descent to lower altitude is not always possible. Moreover, oxygen was used for all patients along with nifedipine, and the effect of supplementary oxygen on alleviating pulmonary artery pressure may have negated any effect of nifedipine in this study population.

Conclusions

Improper acclimatization was the foremost risk factor for the development of HAPE. Soldiers who return to high altitudes after more than 10 days of absence should undergo full acclimatization before ascent to the same altitude. High altitude pulmonary edema is a fairly common problem for soldiers posted at higher altitudes, for mountaineers, and for persons who sojourn to high altitudes for recreation and work.

Acknowledgments

The authors thank Dr Kusum R. Deshwal and Dr Ramakrishnan S. Taramanglam for their sincere and concerted efforts with statistical analysis.

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