Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Original Article

Is it time to revise the acclimatization schedule at high altitude? Evidence from a field trial in Western Himalayas

Gaurav Sikri^{a,*}, Atul Kotwal^b, S.P Singh^c, Srinivasa Bhattachar^d,
S.S Bhatia^e, Manohar Dutt^f, N. Srinath^g

^a Professor and Head, Department of Physiology, Armed Forces Medical College, Pune, 411040, India

^b Dy DGAFMS (Pensions), O/o DGAFMS, Ministry of Defence, 'M' Block, New Delhi, 110001, India

^c Professor, Department of Physiology, Armed Forces Medical College, Pune, 411040, India

^d Assistant Professor, Department of Physiology, Armed Forces Medical College, Pune, 411040, India

^e Commandant, Military Hospital Mhow, C/o 56 APO, India

^f Commanding Officer, 4002 Field Hospital, C/o 56 APO, India

^g Consultant (Surgery), O/o DGAFMS, Ministry of Defence, 'M' Block, New Delhi, 110001, India

ARTICLE INFO

Article history:

Received 5 September 2017

Accepted 2 January 2018

Available online 14 August 2018

Keywords:

Acute mountain sickness

Acetazolamide

Dexamethasone

High altitude

Acclimatization

ABSTRACT

Background: In Western Himalayas, Indian Army soldiers take 11 days (6 days of acclimatization and 5 days of travel) on a sea-level to high altitude road (SH road) to reach a high altitude location (HAL) situated at an altitude of 11,500 feet from sea-level location (SLL) at an altitude of 1150 feet while following acclimatization schedule (AS). AS has an extra safety margin over the conventional 'mountaineering thumb rule' of not exceeding 500 m sleeping altitude above 3000 m altitude. We carried out this randomised field trial to study the feasibility of moving large number of troops rapidly from SLL to HAL on SH road in western Himalayas in 4 days under pharmaco-prophylaxis. **Methods:** Based on the pharmaco-prophylaxis, at SLL 508 healthy lowland soldiers were divided into two groups: 'A' (n = 256) with Acetazolamide + Dexamethasone and 'B' (n = 252) with Acetazolamide + Placebo. They travelled rapidly by road to HAL in 4 days and prevalence of acute mountain sickness (AMS), high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE) during the ascent was measured.

Results: Prevalence of AMS was found to be 1.56% and 1.59% in group 'A' and group 'B' respectively during the ascent with no cases of HAPE and HACE.

Conclusion: At least on SH road, troops can be inducted rapidly to HAL from SLL in 4 days under pharmaco-prophylaxis with Acetazolamide with minimal occurrence of acute high altitude illnesses.

© 2018 Director General, Armed Forces Medical Services. Published by Elsevier, a division of RELX India Pvt. Ltd. All rights reserved.

* Corresponding author.

E-mail address: dr_gaurav35@gmail.com (G. Sikri).

<https://doi.org/10.1016/j.mjafi.2018.01.001>

0377-1237/© 2018 Director General, Armed Forces Medical Services. Published by Elsevier, a division of RELX India Pvt. Ltd. All rights reserved.

Introduction

Indian Army defines high altitude (HA) as any area, which is located at an altitude of more than 9000 ft. These HA areas are further classified as Stage I (9000–12000 ft), Stage II (12,000–15,000 ft) and Stage III (>15,000 ft). To prevent acute high altitude illnesses (HAI) during deployment of troops to HA area, a conventional acclimatization schedule (AS) is being followed by Indian Army for almost last 4 decades now. AS is based primarily on a strategy, which is amalgamation of the conventional staged and graded ascents as practiced by mountaineers. But implementation of a uniform AS for various sectors in HA areas with different ascent profiles could hinder optimum utilization of already limited resources and prolong induction time especially during operations.

Notwithstanding the fact that as per the mountaineering 'thumb rule', a lowlander should not increase his sleeping altitude by more than 500 m beyond 3000 m, AS takes into account an extra margin of safety beyond this 'thumb rule' for lowlander troops during ascent.^{1,2} In Western Himalayas, on a road connecting a sea-level location (SLL) with altitude of 350 m (1150 ft) to a high altitude location (HAL) with altitude of 3500 m (11,500 ft) called in the present study a sea-level to high altitude road (SH road), lowland soldiers take 11 days, which includes 6 days of acclimatization at 9404 ft and 5 days of travel, to reach HAL while transiting through various camps and mountain passes with altitudes ranging from 13,050 to 16,616 ft (Table 1, Fig. 1).

HAI commonly seen at HA are acute mountain sickness (AMS), high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE). Occurrence of these HAI is determined by, rate of ascent, final altitude achieved, previous high altitude exposure and individual susceptibility.^{3,4} Main aim of implementing AS amongst troops is prevention of HAI. Further, the prolonged stay at Stages I and II of HA allows pre-acclimatization for Stage III HA areas, thereby attempting to reduce the burden of disease at areas located at still higher altitudes. Also, it may help in partly restoring exercise capacity (ExC) of lowland soldiers. Physiological processes involved in achieving the benefits of natural acclimatization during AS take time varying from few hours to days⁵ and this might affect the outcome of the task given to lowland soldiers especially during initial period of their stay at HA (Fig. 2).

During operational exigencies requiring movement of large number of troops by road to HA, pharmacological intervention remains an effective modality to prevent HAI.^{1,2} Drugs used mainly for prevention of AMS and HACE are acetazolamide (Acz) and dexamethasone (Dex).^{1,2,6} Dex has also been found to have a preventive role against HAPE at least in susceptible individuals.⁷ With this background, we planned the first phase of the present study to measure the incidence of AMS on SH road while following conventional AS (AS phase). In the second phase of the study, we compared 2 pharmacological regimens (as alternatives to conventional AS) if large bodies of lowland troops were required to move rapidly by road on the SH road while following Rapid road induction schedule (RRIS) (Table 1, Fig. 1).

Table 1 – Comparison of AS with RRIS followed on SH road.

Acclimatization schedule (AS) ^a		Rapid road induction schedule (RRIS)
Day-1	Start from SLL and reach TC0	Start from SLL and reach TC1
Day-2	Start from TC0 and reach/overnight stay at TC1	Start from TC1 and reach TC2 and enter HA (Overnight stay at TC2)
Day-3	Start from TC1 and reach/stay at TC2	Start from TC2 and reach TC3 (Overnight stay at TC3)
Day-4	Stay at TC2 continues and First day of acclimatization commences	Start from TC3 and reach Leh via TC4 (no overnight stay at TC15280)
Day-5–9	Next 5 days of acclimatization at TC2	–
Day-10	Start from TC2 and reach TC15280 via TC3 (no overnight stay at TC3)	–
Day-11	Start from TC15280 and reach HAL	–
Total	11 days	4 days

^a For Stage 1 altitude (>9000 ft) 1st & 2nd day: Complete rest; 3rd & 4th day: Mandatory supervised walk at slow pace for 1.5–3 km without any steep climbs; 5th & 6th day: Mandatory supervised walk at a slow pace for 5 km with a climb up to 300 m.

Fig. 1 – Time line and sleeping altitudes (in feet) during AS and RRIS.

Fig. 2 – Study design.

Material and methods

Participants of the study

Healthy Indian Army male soldiers ($n = 1361$), belonging to battalions of lowland ethnicity and who had not traveled to HA in last 3 years, formed the study group. This randomized control trial (Registration number CTRI/2017/11/010502) was cleared by the Institutional Ethical Committee and performed in accordance with the Declaration of Helsinki. The data collection was carried out between Sep 2011 and Oct 2013 during the 'window period' of summer months when SH road was accessible as this road remains 'cut off' during winter months due to incessant snowfall. The study protocol was explained to all the participants of the study in their respective native language and an informed written consent was taken before including them in the study. This field trial was carried out in two phases and its first phase (AS phase) was aimed to measure the incidence of AMS in lowland Indian troops during their ascent on SH road while following the AS over 6 days. During second phase of the study (RRIS phase), incidence of AMS was measured in participants of two groups ascending while following RRIS aided by pharmaco-prophylaxis. We

hypothesized that the concurrent use of acetazolamide and dexamethasone resulted in lesser fall in ExC than those using acetazolamide alone at HA (Table 1, Fig. 1).

Incidence of AMS during AS phase

To know the incidence of AMS, participants ($n = 794$) were evaluated for AMS using Lake Louise Score (LLS) of self-assessed questionnaire at a transit camp (TC15280) on SH road located at 15,280 ft, which is the highest altitude where troops stay overnight during AS. The self-assessed questionnaire was administered to participants on the morning after overnight stay and the incidence was calculated using 'LLS levels more than or equal to 3'. The moderate-severe form of AMS was taken as LLS more than or equal to 5.^{1,8}

Evaluation during RRIS phase

As part of RRIS phase, one company from each of the Battalion of lowland ethnicity, which was scheduled to ascend to Leh by SH road during the summer months of study period, was selected randomly (by lottery) and soldiers of this selected company were randomly (using random number table)

assigned to one of the groups (A and B). This process was repeated till adequate sample size each group of the study was achieved. A total of 516 participants enrolled for the study at SLL and they were assigned to two groups ($n = 258$ to each of the group 'A' and 'B') after randomization using random number table. Both investigators and participants were blinded from group allocation by the supervisor of the study. There were 08 drop outs (2 from Group 'A' and 6 from Group 'B') from the study due to administrative and logistics reasons. Finally, a total of 508 participants (256 from Group 'A' and 252 from Group 'B') completed the study protocol. They were monitored by a medical team, consisting of experienced medical and paramedical professionals who were trained to identify and treat HA emergencies, throughout the duration of study. Also, occurrence of HAPE and HACE in these participants was actively monitored for next 1 year by keeping a check on records of the central registry of the hospital (located at HAL) providing tertiary level medical care to the battalions included in the study.

Pharmaco-prophylaxis during RRIS (From D – 1 to D + 3)

Participants of Group 'A' (Gp 'A') were given Cap Acz 250 mg slow release (SR) once daily (OD) and Tab Dex 4 mg twice daily (BD) and those of Group 'B' (Gp 'B') were given Cap Acz 250 mg SR OD + Tab Placebo (similar looking dextrose tablets) BD. Pharmacoprophylaxis of both the groups was started on the evening of D – 1 day (penultimate day before exposure to HA on D day) and continued for next 4 days.

Participants of Gp 'A' and Gp 'B' started from SLL by road and reached transit camp 1 (TC1) located at 6600 feet and halted there for one night (D – 1). Next day they were exposed to HA for the first time while crossing a mountain pass located at 13,050 ft and reached transit camp 2 (TC2) located at an altitude of 9404 ft (D day). They stayed over-night at TC2 to move to TC3 (13,850 ft) (D + 1 day) next day. After one night stay at TC3, participants moved to HAL located at 11,500 ft (D + 2 day) (Table 1).

Sample size and subject selection

The reported incidence of AMS in lowlanders after acute ascent beyond 2500 m is 25%.⁹ Also, in unpublished data from one of the project reports of High Altitude Medical Research Centre, the incidence of AMS on SH road was found to be 29%. Thus taking incidence of AMS as 25%, a sample size to assess a difference of 10%, at $\alpha = 5\%$, power = 80%, using the formula $\{[(Z\alpha + Z\beta)^2 \times P \times Q \times 2]/(d)^2\}$ for each group for RRIS phase was worked out to be 251. Thus a total of 502 participants were planned to be studied. Small group of healthy males (number varying from 40 to 80) from various battalions of lowland ethnicity of Indian Army were selected and allotted to Gps 'A' and 'B' using random number table. This process was repeated till adequate sample size in each group of the study was achieved. Any participant with history of allergy to Sulfonamides and those with hypertension or any other morbid condition on screening were excluded from the study group.

Resting heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP),

respiratory rate (RR) and Oxygen saturation (SpO_2) along with LLS and predicted ExC were documented both SLL and HAL.

Measurement of predicted ExC during RRIS phase

At SLL, participants of both the groups of RRIS phase underwent exercise testing on bicycle ergometer for measurement of predicted ExC before ascent and thereafter on D + 3 at HAL. They cycled against initial exercise load of 100 W and maintained a rpm of 50 with an aim to achieve 50–60% of the target heart rate calculated by the formula $220 - \text{age}$ expressed in years. The participant exercised at 100 W for 06 min and heart rate was measured at the end of 5th min and 6th min of exercise phase. If heart rate of 130–170 bpm was achieved by the participant at the end of 6th min and the difference in heart rate was not more than of 5 bpm, mean of heart rates of 5th and 6th minutes was taken and the corresponding final workload was noted for calculation of ExC.

If the heart rate response of the participant was <130 bpm at the initial load of 100 W, the load was increased to 150 W and the whole of the protocol was repeated with an aim of achieving difference of not more than 5 beats between the readings of 5th and 6th minutes. Finally, a nomogram given by Astrand was used to calculate the predicted ExC.¹⁰

Equipment

Multi-parameter Monitor (Schiller's Truscope TM Classic) was used for measuring resting parameters like HR, RR, SpO_2 and BP and load was given to the participants by using Bicycle Ergometer (Monark Ergomedic 839E, GIH Sweden). Heart rate during the exercise phase was measured using heart rate monitor (Polar Electro, Oy Finland).

Analysis

Incidence of AMS during AS and RRIS (both groups) was calculated in percentage and compared by calculating relative risk. All quantitative data was expressed in Mean $\pm$ SD. Means of parameters of two groups of RRIS recorded at SLL and HAL were statistically analyzed using paired 't' test. Unpaired 't' test was carried out to compare the parameters of two groups of RRIS.

Results

AS phase

During ascent based on conventional AS, 152 out of 794 responders at TC 15,280 (19.14%) reported mild AMS and 38 out of 152 had severe AMS (Tables 2 and 3). There was no medical intervention given to mild AMS cases but the severe AMS cases were managed with Acz, paracetamol, rest and descent.

RRIS phase

A total of 508 participants ($n = 256$ for Gp 'A' and $n = 252$ for Gp 'B') completed the study protocol during this phase. The mean

Table 2 – Relative risk for AMS in Group 'A' of RRIS and AS.

	AMS+	AMS–	Total
Gp 'A' RRIS	4	252	256
AS	152	642	794
	156	894	1050
RR = 0.08 (95% CI, 0.03–0.22; $p < 0.0001$).			

Table 3 – Relative Risk for AMS in Group 'B' of RRIS and AS.

	AMS+	AMS–	Total
Gp 'B' RRIS	4	248	252
AS	152	642	794
	156	890	1046
RR = 0.08 (95% CI, 0.03–0.22; $p < 0.0001$).			

age of subjects of Gp 'A' and Gp 'B' was 26.20 ± 4.92 and 26.13 ± 4.68 years respectively. Incidence of AMS during RRIS phase in Gp 'A' and Gp 'B' were 1.56% (4/256) and 1.59% (4/252). Out of 4 cases of mild AMS in both the groups, 3 from each of the groups reported for AMS at TC3 (13,050 ft) on morning of D + 2 while one case each was reported to have AMS in TC2 (9404 ft) during evaluation on the morning of D + 1 day. None of the participants with AMS reported sick on their own and were diagnosed to have AMS during evaluation with self assessed LLS questionnaire before continuing their road journey in the morning along with other non-AMS participants. None of the participants presented with features of HAPE or HACE during the study period or during the next 1 year of active surveillance at the hospital giving tertiary level care to them. Changes in resting physiological parameters seen at HAL are given in Table 4. Data on comparison of various parameters of

participants of Gps 'A' and 'B' are given in Table 5. ExC at HAL fell by 7.83% and 12.97% in Gp 'A' and Gp 'B' respectively in comparison to their SLL findings.

Discussion

Lowland Indian Army healthy soldiers participated in this randomized double blind study and reached HAL in 4 days from SLL while following RRIS on SH road in Western Himalayas. Incidence of AMS was found to be 1.56% and 1.59% in Gps 'A' and 'B' of RRIS respectively and this was statistically lower as compared to incidence observed with AS (19.14%) (Tables 2 and 3). None of the participants developed HAPE or HACE during RRIS. The ExC achieved at HAL on D + 3 was 92.17% and 87.03% of the SLL ExCs in Gps 'A' and 'B' respectively.

During peace time, Indian lowlander soldiers take 11 days, which includes 6 days of AS and 5 days of traveling, to reach HLL from SLL on SH road. During the ascent, they follow a supervised conventional AS which is in vogue for almost 4 decades now. Although the ascent profile of AS is an amalgamation of staged and graded ascents and has extra safety margin over and above the currently suggested limit of not increasing the sleeping altitude by more than 500 m per night above 3000 m, as per WMS guidelines for prevention of acute HA illnesses^{1,2} but practicability of its use in various HA areas having different ascent profiles raises questions in terms of optimum use of limited resources and time taken to reach the final location. This becomes more pertinent when ascent time is at premium for the troops during hostilities. Specifically on SH road, the present study has brought out a safe ascent profile (RRIS) and it can help troops save valuable 7 days in comparison to conventional AS.

Table 4 – Analysis of resting cardiopulmonary parameters of Group 'A' and Group 'B' at SLL and at HAL with paired 't' test.

	Group 'A' (n = 256)		Group 'B' (n = 252)	
	SL	HA	SL	HA
RR (per min)	17.47 ± 2.95	18.86 ± 3.40 ($p < 0.05$)	17.64 ± 2.68	19.35 ± 3.19 ($p < 0.001$)
SpO ₂ (%)	98.98 ± 0.96	94.03 ± 1.73 ($p < 0.001$)	98.89 ± 1.08	93.2 ± 1.9 ($p < 0.001$)
HR (bpm)	61.23 ± 9.87	60.89 ± 11.37 ($p = 0.51$)	61.87 ± 9.21	72.31 ± 11.5 ($p < 0.001$)
SBP (mmHg)	118.11 ± 8.75	120.23 ± 8.65 ($p < 0.05$)	118.01 ± 9.12	117.98 ± 9.31 ($p = 0.80$)
DBP (mmHg)	69.98 ± 8.19	71.09 ± 8.86 ($p < 0.05$)	70.27 ± 8.4	70.81 ± 9.03 ($p = 0.18$)
MAP (mmHg)	83.38 ± 8.17	84.91 ± 8.41 ($p < 0.05$)	83.61 ± 8.49	83.08 ± 8.56 ($p = 0.19$)
ExC (ml/kg/min)	43.7 ± 8.18	40.28 ± 7.73 ($p < 0.001$)	42.72 ± 8.05	37.18 ± 7.33 ($p < 0.001$)

Table 5 – Analysis of resting cardiopulmonary parameters of Group 'A' and Group 'B' at SLL and at HAL with unpaired 't' test.

	SL		HA	
	Group 'A' (n = 256)	Group 'B' (n = 252)	Group 'A' (n = 256)	Group 'B' (n = 252)
RR (per min)	17.47 ± 2.95	17.64 ± 2.68 ($p = 0.49$)	18.86 ± 3.40	19.35 ± 3.19 ($p = 0.09$)
SpO ₂ (%)	98.98 ± 0.96	98.89 ± 1.08 ($p = 0.33$)	94.03 ± 1.73	93.2 ± 1.9 ($p < 0.001$)
HR (bpm)	61.23 ± 9.87	61.87 ± 9.21 ($p = 0.45$)	60.89 ± 11.37	72.31 ± 11.5 ($p < 0.001$)
SBP (mmHg)	118.11 ± 8.75	118.01 ± 9.12 ($p = 0.99$)	120.23 ± 8.65	117.98 ± 9.31 ($p < 0.05$)
DBP (mmHg)	69.98 ± 8.19	70.27 ± 8.4 ($p = 0.69$)	71.09 ± 8.86	70.81 ± 9.03 ($p = 0.73$)
MAP (mmHg)	83.38 ± 8.17	83.61 ± 8.49 ($p = 0.76$)	84.91 ± 8.41	83.08 ± 8.56 ($p < 0.05$)
ExC (ml/kg/min)	43.7 ± 8.18	40.28 ± 7.73 ($p = 0.17$)	40.28 ± 7.73	37.18 ± 7.33 ($p < 0.001$)

Participants of two groups of RRIS reported lower incidence of AMS in comparison to AS and this can have logistic and medical implications on rapid movement of troops on SH road. Rapid movement of troops could result in early availability of troops for duties at HA and save valuable man hours. But for this TCs on SH road shall require to be prepared for faster turn over of the troops. SH road is a seasonal road which remains 'cut off' during winters. Accordingly, ration and fuel storage shall require reinforcement in all the TCs for rapid movement of troops on this road. Communication and medical facilities along the axis require to be augmented along with facilities for air evacuation for optimum medical cover.

AS includes first 2 days of complete bed rest and this is followed by supervised graded exercise over next 4 days (Table 1). During the initial days of AS, the body compensates for the hypobaric hypoxia primarily by hyperventilation aided by increase in hematocrit by hemoconcentration and renal alkaline diuresis.^{11,12} On the other hand, RRIS included 4 days of travel-cum-acclimatization with the help of pharmacological intervention in form of Acz alone (Gp 'B') and in combination with Dex (Gp 'A') with minimal prevalence of AMS. Although the comparison for incidence of AMS during AS and RRIS phases may apparently appear to have been done at different physical altitudes (15,280 ft vs. 13,850 ft), but a physiological equivalence can be drawn between the two ascent schedules. During AS, the difference in altitudes between the highest point of evaluation and sleeping altitude of penultimate night is 5876 ft (15,280–9404 ft), whereas during RRIS, it is 4446 ft (13,850–9404 ft). In spite of this difference (1430 ft/436 m) between both the two scenarios, participants of our study were profiled to have a moderate risk for developing AMS.^{1,2} As per WMS guidelines for preventing AMS in individuals with moderate risk, the participants of AS phase underwent natural pre-acclimatization for 6 nights at 9404 ft and those belonging to two groups of RRIS phase undertook pharmaco-prophylaxis. These two preventive measures possibly placed participants of two phases at comparable levels of risk of developing HAI.^{1,2}

Use of Acz in the present study hastened acclimatization by stimulating frequency of respiration as seen by significant improvement in RR in both the groups of RRIS at HAL. Acz is known to cause a rise in ventilation because of metabolic acidosis caused by inhibition of Carbonic anhydrase.⁶ Dex is known to inhibit cytokines release, attenuate inflammation and also improve vascular integrity in the brain. These effects possibly helped in diminution of cerebral symptoms related to AMS.¹³ Dex has been shown to improve the gas exchange atleast in animals.¹⁴ Moreover, as per the US Special Operations Command guidance, its use as a prophylactic option against HAI has been recommended for Special Operation Forces, especially if they do not have time to acclimatize for HA.¹⁵ A rise of 7.9% observed in RR at HAL in comparison to SLL was possibly because of Dex used in participants of Gp 'A' whereas in the absence of Dex in Gp 'B' 9.7% rise over SLL was seen in RR at HA. A fall of 5% at HAL was observed in SpO₂ of Gp 'A' which was significantly lower than that seen in Gp 'B' (5.75%). Probably these differences can be attributed to addition of Dex in Gp 'A' because of its actions in stimulating alveolar sodium and water clearance thus leading to improved the gas exchange.^{14,15}

At HAL, resting HR increased significantly in Gp 'B' but there was no change seen in HR from SLL to HAL in Gp 'A'. Hypoxia induced sympathetic nervous system stimulation (leading to rise in HR in Gp 'B' at HAL) was nullified by addition of Dex to Acz in Gp 'A' participants.¹⁵ Similar findings were reported by Bernhard et al. while comparing the efficacy of a combination of sustained-release Acz (500 mg OD) and low-dose Dex (4 mg BD) and same dose of Acz alone for prophylaxis against AMS caused by rapid ascent to 5334 m from 3698 m in a double-blind study. They observed greater decrease in SpO₂ and rise in HR after the ascent in Acz alone group as compared to the group given both drugs together.¹⁶

Resting SBP, DBP and MAP of Gp 'A' increased significantly on induction to HAL, however there was no change observed in Gp 'B'. Our findings of lower SBP, DBP and MAP at HAL in Gp 'B', although statistically insignificant, reiterate the observations given by Parati et al., who assessed the hemodynamic changes at HA under the effects of Acz in a randomized double blinded study. They had shown significantly lower values of SBP, DBP and MAP at HA in individuals taking Acz. They had concluded that impact of Acz on the hemodynamic alterations induced by hypobaric hypoxia may be considered as one of the beneficial effects of this drug.¹⁷ In the present study, we had administered Dex for 5 days to participants of Gp 'A' and prolonged use of Dex is known to cause rise in BP due to a general assumption that it causes fluid and salt retention. Other mechanisms implicated in rise of BP with use of Dex are inhibition of the vasodilator nitric oxide system and augmentation of vasoconstrictor erythropoietin concentration.¹⁸ A similar effect of rise in BP has been reported by Whitworth et al. after 5 days use of Dex (8 mg/day) in healthy subjects at SL.¹⁹ In spite of the beneficial effects of Dex against HAI, its use on long term basis for soldiers as a policy decision requires exercise of caution because of its inherent effects like rise in BP, insomnia and impaired decision making.¹⁵

Acz and Dex for their individual effects on ExC at HA have been evaluated but there are not many studies which have evaluated combination of these two drugs on ExC after induction to HA. As per Fulco et al. there is 1% fall expected in ExC for every 100 m above altitudes of 1500 m and therefore the expected fall in ExC located at altitude of 3500 m at HAL in lowland participants of the present study after full acclimatization is 15%.²⁰ We observed a 7.83% fall in ExC in Gp 'A' and 12.97% in Gp 'B' after RRIS. Subjects of both the groups of RRIS stayed at TC3 (13,850 ft) on D + 1 night and could achieve higher ExC than expected at Leh (11,500 ft/3500 m) with the help of pharmacological prophylaxis.

The effects of Acz on ExC in hypoxic conditions have been variable with reporting of decreased,²¹ increased²² and unchanged outcome.²³ In the present study, we have observed lesser fall in ExC than expected with the use of Acz alone (Gp 'B') or in combination with Dex (Gp 'A') after RRIS (Table 5). Schoene et al. reported a rise in ExC with the use of Acz in hypoxic conditions and they attributed the same to increased alveolar and subsequent arterial O₂ tension which may be important for exercise at HA.²² Garske et al. reported fall in ExC in hypoxic conditions with the use of Acz and they brought out the potential mechanisms for reduced ExC include the effect of acidosis on muscle function, dehydration due to diuretic effect, and increased

dyspnea due to stimulation of ventilation.²¹ Dex is known to improve ExC at least in HAPE susceptible individuals at HA as brought out by Fischler et al. and Siebenmann et al. but its effect on ExC of normal individuals at HA has been poorly explored.^{24,25} We evaluated ExC of participants of Gp 'A' using Dex along with Acz and found lesser fall in ExC than expected. This can be attributed to Dex which results in improved ventilation-perfusion ratio and enhanced alveolar Sodium-water clearance responsible for maintenance of ExC.²⁵

Earlier authors, who had evaluated HAPE susceptible individuals at HA, had clarified that findings of HAPE susceptible individuals cannot be applied to general population. However, sub-clinical HAPE is a common phenomenon occurring at HA with incidence varying from 7 to 75% depending on the mode of investigation used to identify it, rate of ascent, genetic susceptibility and amount of physical exertion undertaken at HA.^{26,27} We can speculate that Dex might have the same effect on individuals not susceptible to HAPE, but this will require further studies in allied settings. We reviewed literature for use of Dex and Acz combination for evaluation of changes in ExC at HA without success. Their combined use has been compared with use of individual drug for AMS and resting cardio-pulmonary parameters by other authors but not for ExC especially in non-HAPE susceptible or normal individuals.¹⁶

Our Institutional Ethical Committee did not approve of including a control group in the study which could have followed RRIS with same ascent profile but without any pharmacological intervention in remote HA areas. This is acknowledged as one of the limitations of our study. Also, IEC did not approve of evaluation of our participants for maximal exercise capacity under hypoxic conditions. So, we planned to use a simpler method by giving a sub-maximal load and predicting exercise capacity from heart rate response with the help of a nomogram. The cardiovascular response to sub-maximal exercise in acute hypoxic conditions compared to sea-level is associated with an elevated heart rate with no compromise on stroke volume. This corresponds to an increased cardiac output for the same absolute value of oxygen consumption. This relationship between heart rate and cardiac output is believed to be maintained between 2500 and 4000 m. It is amply clear that the same absolute work rate in hypoxic conditions represents a greater percentage of total oxygen consumption at HA compared to SL and this increase in relative oxygen consumption at HA correspondingly controls cardiovascular response during sub-maximal exercise in hypoxic conditions.¹¹ This prediction test also had certain important advantages in the field scenario of our study. There was no need of sophisticated laboratory and this test did not demand a high degree of cooperation and motivation from the participants. The individual was not required to cycle with maximal effort particularly when participants of our study had spent only 4 days at HAL before evaluation. Moreover, each participant required 10–14 min for complete evaluation which also included measurement of resting cardio-pulmonary parameters. The number of participants evaluated varied from 40 to 80 per day making a prediction test a preferred method for calculation of ExC.

We used Astrand nomogram, for measurement of ExC through HR response, which is a validated protocol at sea level

with a standard error for prediction of maximal Oxygen uptake from sub-maximal exercise test, which is estimated to be 10% in well trained and up to 15% in moderately trained individuals.²⁸ As our participants were Indian Army soldiers and considering them as moderately trained individuals, mathematically a conservative correction factor of 15% can be applied to the ExC predicted in the study using sub-maximal protocol. With application of this correction factor at HA, the ExCs achieved by participants of Gps 'A' and 'B' will be 78.34% and 73.98% respectively of their SL capacities. This gave us a rough estimate of their ExCs and depending on their work profile depending on trade, further field tests are suggested to be carried out in field scenarios.

We believe that drugs used for pharmaco-prophylaxis against HAI may not be a practicable option for ExC 'enhancement' at HA. Use of these drugs should remain limited to prevention of HAI. Although we did not come across any side effects of these drugs in our study groups but keeping in mind the reported side-effects, pre-acclimatization should be a preferred modality for prevention of HAI especially during peace time.^{1,2}

To summarize, lowlander males following RRIS with pharmacological intervention reached HAL in 4 days from SLL and saved valuable 7 days on SH road in comparison to the usual 11 days of AS with minimal occurrence of AMS. Predicted ExC achieved with RRIS at HAL was similar in both the groups and was comparable to the expected levels after complete acclimatization based on current literature. To conclude, the present study clearly brings out that a 'customized tailor made' schedule like RRIS, as an alternative to AS, exists atleast on SH road for use during exigency conditions. A time has come to develop and validate similar axis specific, rapid induction schedules for use at a particular axis for induction of troops to HA areas. This schedule can be implemented during operational exigencies keeping in mind the existing logistics and administrative resources available on that axis. However, during the peace time, the robust and time-tested conventional AS can continue to be in vogue without any revision.

Conflicts of interest

The authors have none to declare.

Acknowledgements

a) This paper is based on Armed Forces Medical Research Committee Project No. 4063/2010 granted by the office of the Directorate General Armed Forces Medical Services and Defence Research Development Organization, Government of India.

b) The authors acknowledge Lt Gen (Retd) Mandeep Singh, Col (Retd) SS Gill, Lt Col (Retd) Latika Mohan, Maj Gen RS Grewal, Maj Gen Sagarika Patyal, Maj (Retd) Manvinder Tejpal and Maj Ritesh Acharya for logistics, administrative and medical support provided during data collection. The contribution of medical officers and para-medical staff of High Altitude Medical Research Center (Leh) is also acknowledged.

REFERENCES

1. Luks AM, McIntosh SE, Grissom CK, et al. Wilderness medical society consensus guidelines for the prevention and treatment of acute altitude illness. *Wilderness Environ Med.* 2010;21:146–155.
2. Luks AM, McIntosh SE, Grissom CK, et al. Wilderness medical society practice guidelines for the prevention and treatment of acute altitude illness: 2014 update. *Wilderness Environ Med.* 2014;25:S4–S14.
3. Waeber B, Kayser B, Dumont L, et al. Impact of study design on reported incidences of acute mountain sickness: a systematic review. *High Alt Med Biol.* 2015;16:204–215.
4. Schneider M, Bernasch D, Weymann J, Holle R, Bärtsch P. Acute mountain sickness: influence of susceptibility, pre-exposure, and ascent rate. *Med Sci Sports Exerc.* 2002;34:1886–1891.
5. Muza SR, Beidleman BA, Fuco CS. Altitude pre-exposure recommendations for inducing acclimatization. *High Alt Med Biol.* 2010;11:87–92.
6. Leaf DE, Goldfarb DS. Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness. *J Appl Physiol.* 2007;102:1313–1322.
7. Maggiorini M, Brunner-La Rocca HP, Peth S, et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. *Ann Intern Med.* 2006;145(7):497–506.
8. Roach RC, Bärtsch P, Hackett PH, et al. The Lake Louise consensus on the definition and quantification of altitude illness. In: Sutton JR, Coates G, eds. *Hypoxia and Molecular Medicine*. Burlington, VT: Queen City Press; 1993:327–330.
9. Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med.* 1993;118:587–592.
10. Sikri G, Srinivasa AB, Grewal RS. Does concurrent prophylactic use of acetazolamide and dexamethasone bring change in exercise capacity of lowlanders on ascent to high altitude? *Indian J Physiol Pharmacol.* 2014;58(1):87–91.
11. Wolfel EE, Levine BD. The cardiovascular system at high altitude. In: Hornbein T.F., Schoene R.B., eds. *High Altitude: An Exploration of Human Adaptation*. New York: Marcel Dekker; 2001:235–292.
12. Smith AS, Dempsey JA, Hornbein TF. Control of breathing at high altitude. In: Hornbein TF, Schoene RB, eds. *High Altitude: An Exploration of Human Adaptation*. New York: Marcel Dekker; 2001:139–173.
13. Bärtsch P, Roach R. Acute mountain sickness and high altitude cerebral edema. In: Hornbein TF, Schoene RB, eds. *High Altitude: An Exploration of Human Adaptation*. New York: Marcel Dekker; 2001:731–776.
14. Stelzner TJ, O'Brien RF, Sato K, Weil JV. Hypoxia-induced increases in pulmonary transvascular protein escape in rats: modulation by glucocorticoids. *J Clin Invest.* 1988;82:1840–1847.
15. O'Hara R, Serres J, Dodson W, et al. The use of dexamethasone in support of high-altitude ground operations and physical performance: review of the literature. *J Spec Oper Med.* 2014;14(4):53–58.
16. Bernhard WN, Schalick LM, Delaney PA, Bernhard TM, Barnas GM. Acetazolamide plus low-dose dexamethasone is better than acetazolamide alone to ameliorate symptoms of acute mountain sickness. *Aviat Space Environ Med.* 1998;69:883–886.
17. Parati G, Revera M, Giuliano A, et al. Effects of acetazolamide on central blood pressure, peripheral blood pressure, and arterial distensibility at acute high altitude exposure. *Eur Heart J.* 2013;34(10):759–766.
18. Whitworth JA, Mangos GJ, Kelly JJ. Cushing, cortisol and cardiovascular disease. *Hypertension.* 2000;36:912–916.
19. Whitworth JA, Gordon D, Andrews J, Scoggins BA. The hypertensive effect of synthetic glucocorticoids in man: role of sodium and volume. *J Hypertens.* 1989;7:537–549.
20. Fulco CS, Rock PB, Cymerman A. Maximal and sub-maximal exercise performance at altitude. *Aviat Space Environ Med.* 1998;69:793–801.
21. Garske LA, Brown MG, Morrison SC. Acetazolamide reduces exercise capacity and increases leg fatigue under hypoxic conditions. *J Appl Physiol.* 2003;94:991–996.
22. Schoene RB, Bates PW, Larson EB, Pierson DJ. Effect of acetazolamide on normoxic and hypoxic exercise in humans at sea level. *J Appl Physiol.* 1983;55(6):1772–1776.
23. Faoro V, Huez S, Giltaire S, et al. Effects of acetazolamide on aerobic exercise capacity and pulmonary hemodynamics at high altitudes. *J Appl Physiol.* 2007;103:1161–1165.
24. Siebenmann C, Block KE, Lundby C, Nussbamer-Ochsher Y, Schoeb M, Maggiorini M. Dexamethasone improves maximal exercise capacity of individuals susceptible to high altitude pulmonary edema at 4559m. *High Alt Med Bio.* 2011;12:169–177.
25. Fischler M, Maggiorini M, Dorschner L, et al. Dexamethasone but not tadalafil improves exercise capacity in adults prone to high altitude pulmonary edema. *Am J Respir Crit Care Med.* 2009;180:346–352.
26. Cremona G, Asnaghi R, Baderna P, et al. Pulmonary extravascular fluid accumulation in recreational climbers: a prospective study. *Lancet.* 2002;359:303–309.
27. Sikri G, Prasad BAK, Muthanna BA, et al. Sub-clinical high altitude pulmonary edema in lowlanders at 3600 m: an observational study. *Indian J Physiol Pharmacol.* 2017;61(1):80–83.
28. Astrand P, Rodahl K. *Textbook of Work Physiology*. 3rd edition Singapore: McGraw-Hill Book Co.; 1986.