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Pen Paper & A Pulse Oxymeter: Prospective Study of the Effect Acetazolamide Have in Quick Trans-Himalayan Acescent

Authors
Dr Sourav Iswarari MBBS, MD (PM&R)[1], Dr Ushnish Mukherjee MBBS[2], Dr Rachit Gulati MBBS[3], Dr Jayanta Kumar Rout MBBS, MD (Biochemistry)[4], Dr Tapobrata Guha Ray MBBS, MD (Community Medicine)[5]

[1]Associate Professor, Department of Physical Medicine and Rehabilitation, R.G.Kar Medical College and Hospital, Kolkata (West Bengal), India
[2]Post Graduate Trainee MBBS, (PM&R), Department of Physical Medicine and Rehabilitation, R.G.Kar Medical College and Hospital, Kolkata (West Bengal), India
[3]Post Graduate Trainee, (PM&R) Department of Physical Medicine and Rehabilitation. R.G.Kar Medical College and Hospital, Kolkata (West Bengal), India
[4]Assistant Professor, Department of Biochemistry, R.G.Kar Medical College and Hospital, Kolkata (West Bengal), India
[5]Associate Professor, Department of Community Medicine, R. G. Kar Medical College and Hospital, Kolkata (West Bengal), India

Corresponding Author
Dr Sourav Iswarari
MBBS,MD(PM&R), Associate Professor, Department of Physical Medicine and Rehabilitation, R.G.Kar Medical College and Hospital, Kolkata (West Bengal), India.
Address: Flat A/1, Usashi, Bindubashini Co-operative, Block Q/67, BP Township, Kolkata-94. West Bengal, India
Email: *physiatristonline@gmail.com, Phone: +91 9433773111*

Abstract

Introduction: *Two Bengali mountaineering team of expeditionist one from Kolkata, India other from Bangladesh took part in a study to determine the effect of acetazolamide by easily usable parameters in quick high altitude sojourns .The aim was also to see if data collected can be used by layman expeditionist for meaningfully accessing team's condition thereby making rational choices in such wilderness.*

Materials & Methods: *Two expeditions were conducted separately in the same region of Trans Himalayan high altitude deserts of Northern most Spiti in Himachal Pradesh, India. Those who had any acute or chronic illness, patients on regular medications, and those who had sojourns at an altitude > 2500 meters during the previous 4 weeks, age < 20 or > 60 years and hemoglobin concentration < 12.0 g/dL were not involved in the study. Sojourns were attempted at month of July/August in two consecutive seasons. In group 1 from Kolkata 13 subjects were put on acetazolamide. The regimen was to take 125 mg acetazolamide twice daily. In group 2 from Bangladesh had 9 subjects who did not opt for medical prophylaxis by choice. During high-altitude exposure, resting measurements of peripheral capillary oxygen saturation (SpO2), heart rate (HR) and Lake Lewis Score (LLS) were taken in the evening of 1st, 2nd, 5th day, 6 Th and 8th day*

starting from 293 meter and ending in 5200 meter as subjects climbed relentlessly.
Results: *Average age in group 1 was 43.08 ± 11.62 years (range: 25 to 65 years) while that of group 2 was 30 ± 4.74 years (range: 23 to 36 years). All were males. RANK tests are done for data which were not normally distributed and analyzed by Man-Whitney U. This showed significant difference of LLS noted between two groups at 3910 m only. The group under acetazolamide prophylaxis showed significant better outcome then ones without it. In independent sample test of parametric data, t-test for equality of means revealed Sp02 (t=4.616) and HR (t=-3.486) had highly significant changes .The group who were not given acetazolamide prophylaxis showed comparative increase in HR and decreased Spo2 at that critical altitude which were statistically significant.*
Conclusion: *Acetazolamide was shown to further the process of acclimatization at a critical time-line and altitude window. The study in the process was able indicate definable relationship between various parameters at different altitudes which were in concurrence with physiological responses.*

Introduction

Acute exposure to high altitude hypoxia in unacclimatized low landers causes various physiological alterations. Among them ventilatory response is considered the most crucial pivot point determining successful sojourns into thin air. Two main types of physiological response are at interplay namely the peripheral hypoxic ventilation response (HVR) and the central hypercapanic ventilatory response (HCVRs) [(1)]. HVR driven by peripheral chemo receptors is responsible for 30 % of ventilatory drive [(1)] whereas HCVRs is responsible for 70% of the ventilation operating through central receptors. HCVRs respond to CSF proton concentration (acidosis) [(1,22)]. Hence ventilation is regulated principally by arterial partial pressure of O2, CO2 (PO2, PCO2) & blood Ph variables controlling HVR and HCRVs response [(1,22)].

CA inhibitor acetazolamide acts on both HVR & HCVRs. In altitudes at excess of 3500 meter body's ability to produce adequate protons in CSF is decreased by initial HVR which washes away CO2 thereby dampening HCVR [(22)]. It cuts down HVR at initial exposure to high altitude [(30)]. It also induces metabolic acidosis to counter the respiratory alkalosis that happens immediately after exposure to high altitude. Acetazolamide serves a prophylactic role when one attains a fixed altitude [(19)]. There is still varied opinion on its mechanism of action though [(31)]. There have been studies on effective dosage of Acetazolamides [(25)] and its role in Acute Mountain sickness has been recognized [(19)]. Hence an enquiry about role of acetazolamide in quick assent where altitude changes every other day was a novel idea for consideration.

Other important component of enquiry was autonomic and cardiovascular alteration working in tandem with ventilatory response [(9,10,13,14)]. It has been proposed recently a mathematical model of these variables needs to be established in order to predict and prognosticate the process of acclimatization [(26)]. For that a study was imperative in establishing relationship between ventilatory and cardiovascular systemic responses from easily observable clinical data itself. A model consisting of a simple intervention like acetazolamide could be easily conducted. A prospective comparative study of group with and without acetazolamide prophylaxis on data like Spo2, heart rate & LLS (Lake-Louise-Score) of subjects rapidly ascending to high altitude seemed feasible with just a pen, paper and pulse oxymeter. For this we recruited two Bengali mountaineering team of expeditionist one from Kolkata, India other from Bangladesh. The expedition was conducted at the same region of Trans Himalayan high altitude deserts in Northern Spiti, Himachal Pradesh, India. The trail into the headwaters of Karcha nullah glacier system B at a height above 5000 meter was decided to be field of study. Two consecutive season of climbing under similar seasonal condition was undertaken. The Kolkata group was placed under acetazolamide while the Bangladeshi group did not opt for any medications.

Objective

1. Role of acetazolamide on LLS score, Heart Rate and SpO2 on relentless acescent.
2. Observation of changes in various altitudes for Bengali population.
3. Correlating finding of LLS, Sop 2, and Heart rate data with altitude within the groups and across group.

Methods

Fifteen volunteers with previous exposure to similar altitude were recruited for this study from Kolkata in 2014. Sojourns were attempted in month of August. Subjects were put on acetazolamide regimen as given below. One was not considered for study as he suffered a fall during 1st days trek and had to be treated. Fourteen reached Base camp at 4800 m. Of them eleven reached Camp 1 on glacier B at 5200 m. Summit attempt was made by 10 members but they were not successful for technical reasons. Eleven volunteers with previous exposure to similar altitude were recruited for this study from Bangladesh in 2015. Expedition was carried in end of July. The subjects of this group were not under medical prophylaxis of their own volition. In case of an AMS (Acute Mountain Sickness) developing or as per team medic's opinion whichever the case they were free to take medications and were automatically to be considered out of study. Two developed AMS and chose to be medicated, while one opted for acetazolamide citing sleeping concerns. Thus only 9 were considered for enquiry that made it to Base camp at 4800 m. Of them only 4 were able to go on the glacier B and establish Camp 1at 5200m. These 4 climbers interestingly went on to climb Mt Cheema at 6105 m.

Exclusion Criteria

Those who had any acute or chronic illness, patients on regular medications, those who had sojourns at an altitude > 2500 meters during the previous 4 weeks, age < 20 or > 60 years and hemoglobin concentration < 12.0 g/dL were not involved in the study. Subjects who were not on prophylaxis if developed signs and symptoms of any sickness were to be taken off study. They were treated or discharged from expedition to low altitude accordingly. Written informed consent was obtained from each subject after full disclosure of the study.

Plan of Expedition

Plan of expedition for both party were exactly pre-programmed and executed. It was as follows. After routine examination at Delhi at an altitude of 293 meter subjects were transported overnight to Manali by car at an altitude of 1941 meters. They spent 2 days there making arrangements for logistics. From there parties were transported to Batal by car at an altitude of 3910 m where they rested for 2 days. The parties trekked from road head along bank of glacial stream Karcha to establish intermediate camp (IC) at 4300 m. On the 5th day party climbed to base camp at 4830 m .On 8th day the target altitude of 5200 m (Camp 1) was achieved and the parties established camp on Glacier-B.

The study participants on prophylaxis were started on acetazolamide 2 day prior to exposure at high altitude, the 2015 group of Bangladeshi expeditionist were not given any medication.

Study Location shot from 5500 meters. Glacier B on right with Mt Cheema (6,105m) at its end.

Glacier system C left with Mt Ache (6066 m) at head. Moraine scree zone with glacial stream emanating from the snout forming the headwaters

of Karcha Nullah. Location belongs to Kullu administrative district of the State of Himachal Pradesh, India. But the access route is from Batal in Lahul administrative district of Himachal Pradesh. Karcha Nullah is a small river about 17 km long located at an approximate co-ordinates of N32° 20'.

Acetazolamide Regimen

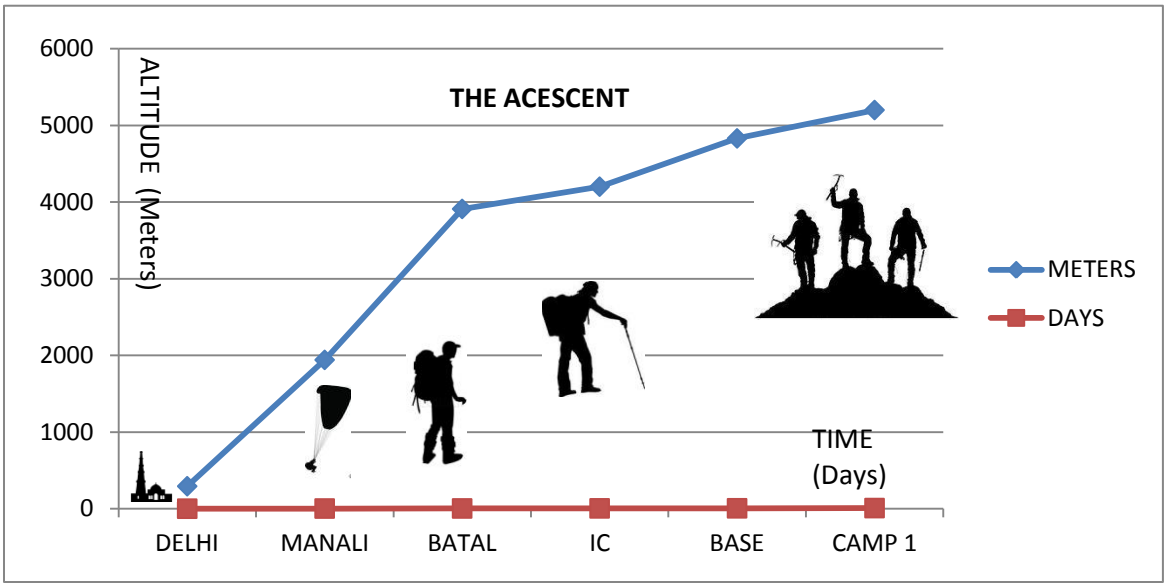
Subjects on prophylaxis received one 125 mg acetazolamide tablet to be taken twice a day [35] .The dosage schedule was decided after consulting previous studies [33,34,35,3,4,5,6,19]. Tablets were administered by an appointed person who ensured the timely intake of tablets. All scoring were done in evening after the party has rested adequately for baseline measurement. During high-altitude exposure, resting measurements were conducted in the evening of the first, the third day, 5th day, 6 Th days and 8th day at different altitude as mentioned. Resting measurements were performed after a 10-minute rest in sitting position inside warm mess tent .Care was taken to keep hands warm by prior wearing of mittens .Stability and amplitude of finger pulse oxymetry was standardized [36]. A brief evaluation of AMS symptoms according to the LLS was also enquired [32]. Participants did limited physical activity at Manali and Batal. Once on trail activities included rigorous 6 to 7 hours of hiking, fording streams, tent pitching and cooking. Every member was instructed not to exceed individual perceived intensity of about 14 on the Borg Scale during the process. Nutrition and sleep were standardized for both groups who enjoyed similar cultural and culinary habits.

Statistical Analysis

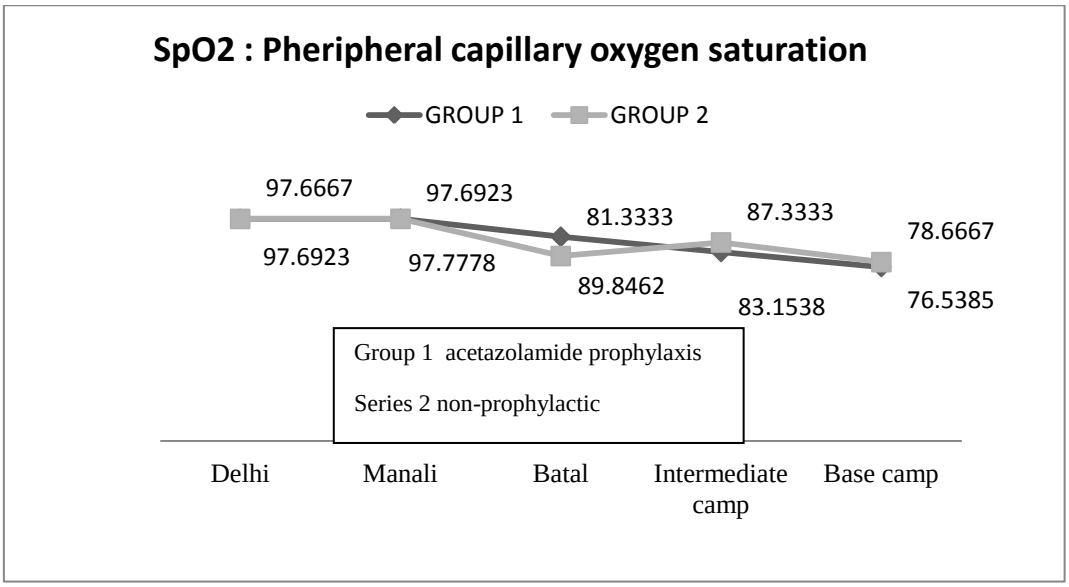
Statistical analysis were done in windows excel 2013. Descriptive statistics were as follows. Average age in group 1 was 43.08 ± 11.62 years (range: 25 to 65 years) while that of group 2 was 30 ± 4.74 years (range: 23 to 36 years). All were males. At New Delhi (293m) mean SpO2 in group 1 was 97.69 ± 0.63 (range: 97-99) while that in group 2 was 97.67 ± 0.71 (range: 97-99).Mean Heart Rate in group 1 was 72.61 ± 8.1 (range: 60-94) while that in group 2 was 71.33 ± 5.24 (range: 61-78).LLS in both groups was 0.At Manali (1941m) mean SpO2 in group 1 was 97.69 ± 0.63 (range: 97-99) while that in group 2 was 97.78 ± 0.83 (range: 97-99).Mean Heart Rate in group 1 was 74.08 ± 7.6 (range: 61-94) while that in group 2 was 71.44 ± 5.7 (range: 60-78).LLS in both groups was 0 except one subject of group 2 having LLS = 1.At Batal (3910m) mean SpO2 in group 1 was 89.85 ± 3.53 (range: 84-97) while that in group 2 was 81.33 ± 5.14 (range: 74-93).Mean Heart Rate in group 1 was 80.07 ± 14.93 (range: 55-105) while that in group 2 was 100.11 ± 10.22 (range: 90-119).Mean LLS in group 1 at Batal was 0.92 while that of group 2 was 4. At Intermediate Camp (4300m) mean SpO2 in group 1 was 83.15 ± 5.77 (range: 75-92) while that in group 2 was 87.33 ± 4.21 (range: 81-93).Mean Heart Rate in group 1 was 106.46 ± 16.78 (range: 84-134) while that in group 2 was 100 ± 5.61 (range: 93-110).Mean LLS in group 1 at Intermediate Camp was 1.00 while that of group 2 was 1.11.At Base Camp (4800m) mean SpO2 in group 1 was 76.54 ± 9.5 (range: 52-90) while that in group 2 was 78.67 ± 6.08 (range: 71-89).Mean Heart Rate in group 1 was 99 ± 13.49 (range: 78-118) while that in group 2 was 106.78 ± 9.37 (range: 97-123).Mean LLS in group 1 at Base Camp was 2.23 while that of group 2 was 2.67

Test of normality done for all the variables, but only the Spo2 at Delhi (293m) , LLS at Batal (3910m) , LLS at Intermediate Camp (4300m), LLS at Base Camp(4800m) , Sp02, Heart Rate and LLS at the Camp 1 (5200 m) follow the normal distribution. RANK tests are done for data which were not normally distributed and analyzed by Man-Whitney U which shows only significant difference of LLS noted between two groups at Batal Camp (3910m) with the group under acetazolamide prophylaxis showing significantly better scores than ones without it. In independent sample test of parametric data, t-test for equality

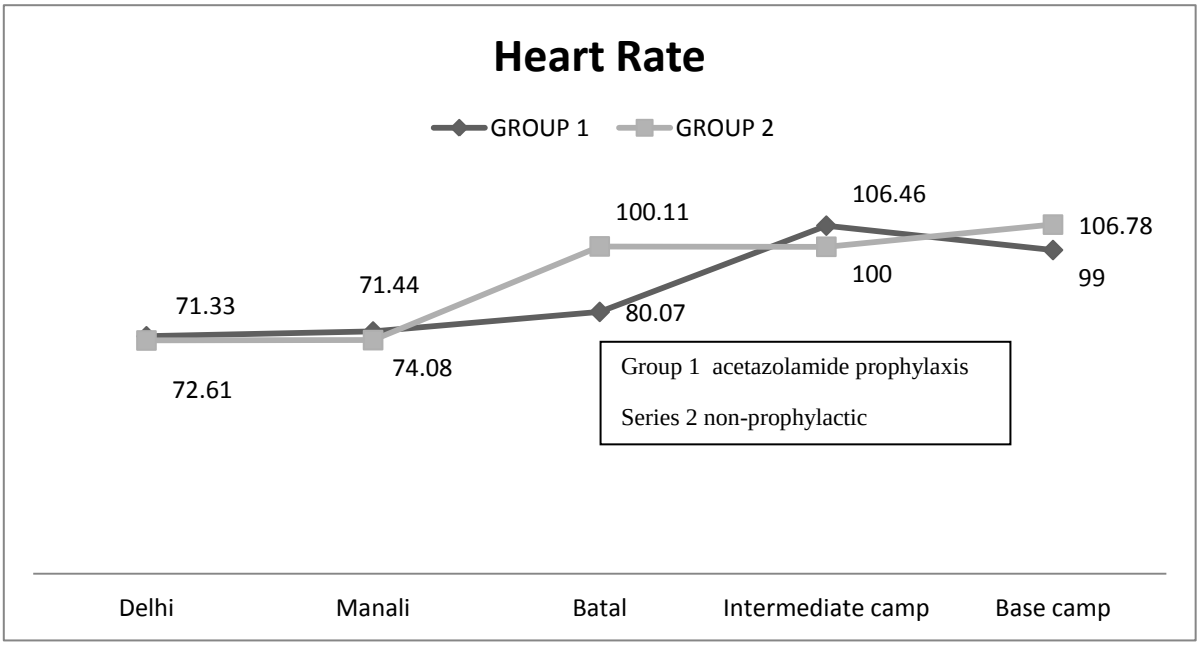
of means reveals t=4.616 for Sp02 measures in Batal at 3910 m .At similar altitude HR had t=-3.486. These values suggested highly significant changes. The group who were not given acetazolamide prophylaxis showed comparative increase in HR and decreased Spo2 at that critical altitude which was statistically significant.



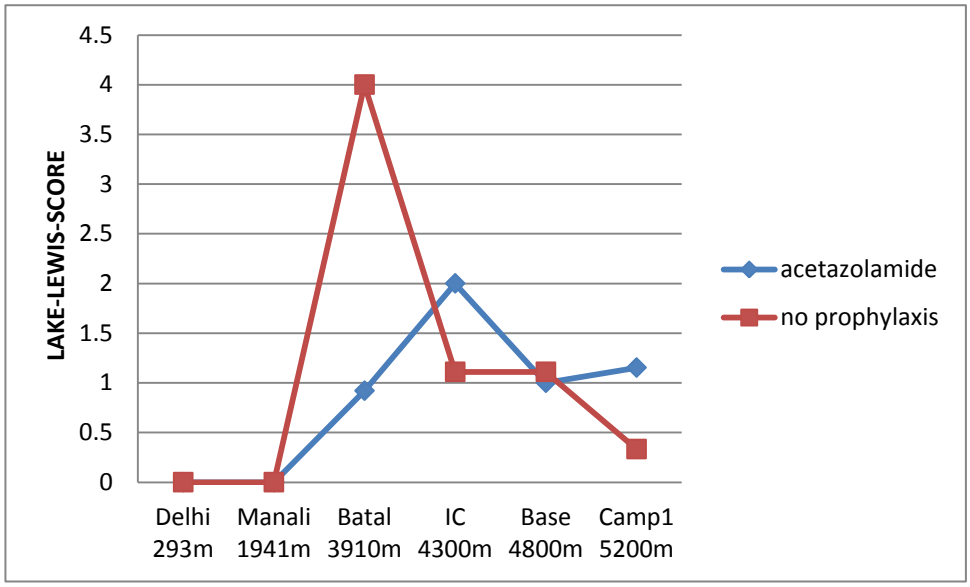
The Trans-Himalayan Plot: A graphical representation for the plan of expedition, altitude gained vs. days.



Mean SpO2 values at different camps from Delhi to Base Camp



Mean HEART RATE values at different camps from Delhi to Base



Average Lake Lewis values at different altitude from Delhi to Camp 1

Discussion

It is available knowledge that when an unacclimatized low lander goes to high altitude, with in the first few minutes peripherally driven HVR increases ventilation resulting in fall of Pco2. This dampens the central ventilatory drive for 20 to 30 minutes. After that for days to week the ventilation increases despite of Pco2 reduction which forms the basis of successful respiratory acclimatization [(1)]. It has been seen in studies that the CSF of unacclimatized low lander originally have a HCO3 level of 24.7 Mm, this value decrease to around of 19.1 -21.3 at altitudes of 4880 m as he completes acclimatization which is comparable to high landers adapted at high altitudes [(27,28,29)]. It takes about a week for the HCO3 values to reach lower level mentioned. So it is within this interim period of days to week the lowlander find themselves most vulnerable to Acute mountain sickness (AMS) or sometimes something even worse. The study attempted to see what exact effect acetazolamide have on

acclimatization and more importantly find relations between various easily acquired data we collected by pen paper and pulse oxymeter at various altitude brackets as the subjects ascended in a quick relentless fashion .

Significant difference of LLS noted between two groups at 3910 m with the group under acetazolamide prophylaxis showing significant better acclimatization than ones without it. As stated the group who were not given acetazolamide prophylaxis showed comparative increase in HR and decreased Spo2 at 3910 m. It was revealed that an altitude of 3900 meters is significant in acclimatization process as is the range of climb from 1941 m to 3910 m. The speed of ascent in a single day covering such range was physiologically and symptomatically telling on subjects not under prophylaxis compared to whom who took it. Such can be explained by acetazolamide induced acidosis which improves tissue oxygen availability and subsequently eases the subject from hypoxia induced drive to increase cardiac output. This increase in cardiac output reflected in observable significant increase in heart rate for subjects not on acetazolamide [9,10, 13,14,15,18,22]. However we didn't measure the blood ph to ascertain exact values by making that assumption relaying on competent authorities [22]. This intuitive approach was sought to keep the study non-invasive and user-friendly.

Significantly better capillary oxygenation (spo2) is observed at this altitude in those on prophylaxis corroborating with literature showing improved arterial and capillary oxygenation [16,17,18,20,21,22,36]. What proportion of it was due to its dampening of HVR [23,24] or due to HCVR or otherwise we could not infer from the nature of data retrieved ,having said that it must be pointed that Acetazolamides action on HVR and sleep has been well researched [30] and performance of sleep do form an essential part of LLS. Another component LLS is headache which can't be clinically distinguished from headache of sleep deprivation and lassitude arising from HVR. Acetazolamide induced decreased HVR hence can contribute to better subjective LLS. It can be actively speculated from our data that HVR dampening did appear to help majority subject who took prophylactic though not possible to objectively specify from current data. Many other factors induced by hypoxia were found in previous studies but the exact interaction of acetazolamide with these factors is now open to speculation beyond the scope of present investigation [11].

4300 meters

Interestingly after a certain critical height of 4300 m was attained at 5th day no significant difference between LLS was observed between groups. Induced acidosis didn't seem to act deferentially as it did around 4000 m. Extreme rapidity of accent needs considerable consideration. LLS in prophylactic group showed increase mean scores while those in non prophylactic group average scores came down. So the non prophylactic group did clinically better and seems to recuperate in this next day's climb. Then prophylactic group however were showing higher scores then they did the previous day before. We found that the mean Spo2 values of prophylactic group dropped while that of non-prophylactic group increased compared to previous altitude but there were no significant difference among them. How ever again heart rate values in prophylactic group increased and that of non-prophylactic group decreased compared to previous altitude. It is a matter of ripe conjecture that the beneficial effect of acetazolamide seemed to be wearing off, oxygen debt seems to have hit the physiologic ceiling and the only course in face of mounting challenge for the system is adjust to hypoxic stress at this altitude window is by decreasing the energy cost and activation of complex pathways [11]. One such response is by cutting down pathways of adrenergic stimulation at windows above 4000 meters [7,8,13,14,15]. Decreasing tissue utilization of oxygen by metabolic alteration is another [7,8,13,14,15]. These two mechanism might be considered in context, other two coping mechanism are by increasing blood viscosity and

reduction in blood volume. So in nutshell the body reduces its cardiac output and aerobic capacity in face of increasing hypoxia to cope with such relentlessly hostile environment [7,8]. Our finding can implicate the above theory .The relation between various measurable parameters and LLS needs be sought and established in more comprehensive manner for us to prognosticate on such clinical finding in more robust fashion.

A relationship between LLS and SpO2 and heart rate could be thus arrived at by these two sets of observation. Rudimentarily the study points to a directly proportional relationship existing between HVR and heart rate along with an inversely proportional relationship existing between HCVR and heart rate in hypoxia challenged state. Which of the two is of significance can't be resolved from our study but certainly we were able to quantify the altitude range and time-span window when a low lander is most vulnerable.

4800-5200 meters

We found heart rate seem to drop from initial high but have no significant difference amongst groups so it can be safely claimed the tonic response of heart rate comes down as subject ascends independent of intervention [11,12], one intriguing observation can be made from heart rate values (though statistical significance can't be claimed) is that the prophylactic group though held up heart rate up to 4800 m but at altitude of 5200 m it seem to lag behind the non prophylactic group who seem to maintain a better tonal control of heart rate. From which an assumption can be ventured that acetazolamide might have some damping effect on tonal heart rate at altitude of more than 5000 m. This morsel of observation can be studied in future with an adequately designed investigation. When we add the time dimension to gaining height we find that there seems to be gradual improvement of LLS values beyond 5th day of relentless climb. This is indicative of acclimatization as function of time. To sum up we detected three windows with perturbed values of parameters studied. Window at 3rd day camp on 3900 m can be significantly altered with acetazolamide whereas other at 5th day on 4200 and 7th day on 5200 m were not significant between two groups.

In the light of this simplistic study with intuitive assumption from previous knowledge it can be pointed that acetazolamide was effective in furthering the physiologic acclimatization of low landers from Bengali recreational high altitude sports enthusiast community only at a particular critical altitude and time variable window. Beyond that critical window the human physiology adapts to altitude somewhat independent of induced acidosis by acetazolamide.

Conclusion

Acetazolamide was shown to further the process of acclimatization at a critical time-line and altitude window. The study in the process was able indicate definable relationship between various parameters at different altitudes which were in concurrence with physiological responses.

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Sudipto Paul, Graduate of Advanced Mountaineering, Nehru Institute of Mountaineering, Professional Climber and Mountain guide, Team leader of both expeditions.

Summiteers registered mountaineering club affiliated to Himalayan Mountaineering Association, India.

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