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Effect of Intermittent Normobaric Hypoxia Exposures on Acute Mountain Sickness during Acute Ascent to 3500 m in Indian Army Personnel

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ABSTRACT

In emergencies/war like situations, rapid deployment of army personnel into high altitude occurs without proper acclimatisation. Rapid movement of unacclimatised soldiers to high altitude may have deleterious effects on the operational capabilities coupled with incidences of acute mountain sickness (AMS). Altitude acclimatisation is the only solution to avoid AMS. Use of pharmacological intervention for prevention of AMS is a common practice. The use of intermittent hypoxic exposure (IHE) is an alternative approach for altitude acclimatisation as it reduces occurrence and severity of AMS. The use of intermittent normobaric hypoxia exposure at sea level on occurrence of AMS after acute ascent to 3500 m altitude in Indian army personnel has not been tested yet.

Keywords: High altitude; Intermittent normobaric hypoxia; Acute mountain sickness

1. INTRODUCTION

High altitude (HA) is defined as 9000 ft (>2400 m) and above because at this altitude most of the people develop sign and symptoms which are associated with acute mountain sickness (AMS). Low landers residents (<1500 m) rapidly ascending to high altitude (>2400 m) and specially at very high altitude are at risk of developing high altitude illness i.e; Acute mountain sickness (AMS). If medical attention is not sought, this may lead to life threatening high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE). The symptoms of AMS occur within few hours after ascent and become prominent after first night spent at high altitude. If further ascent is not attempted, the resolution of AMS occurs by 2 – 3 days of residence. In emergencies/war like situations, military personnel could be inducted to high altitude within a short time and may be deprived from appropriate acclimatisation. As a result, some of them are at risk for physical problems related to high altitude disorders, which could be unpleasant and may even lead to fatal casualties[1]. In our earlier studies we observed the effect of altitude on heart rate variability[2], cardiovascular response[3], respiratory physiology[4], chemoreceptor sensitivity[5,6], sub-maximal and maximal exercise responses[7,8] through the preliminary days of acclimatisation at different altitudes. At high altitude, a sequence of pulmonary and cardiovascular alteration occurs to maintain sufficient oxygenation of the different systems like, increase in heart rate, cardiac contractility and cardiac output. The critical initial adaptive changes to altitude induced hypoxemia are pulmonary artery vasoconstriction and peripheral and cerebral artery vasodilatation at the vascular level[3]. The altitude induced exhilaration of cardiovascular system comes to its maximum effects during the initial few days and progressively establishes a steady state condition[3]. After these modifications have reached the optimal level, any further stimulation may have harmful effects and may cause high altitude related diseases like HAPE or HACE[1]. Immediate response to high altitude is augmented ventilation and considered to be one of the most important indices of altitude acclimatisation. Ventilatory acclimatisation to altitude is characterised by progressive increase in ventilation that leads to an increase in pulmonary gas exchange and oxygen saturation level. Augmented ventilation and diuresis during the initial few days at high altitude may contribute to easing of AMS symptoms with altitude acclimatisation[9]. Acetazolamide is the 'gold standard' pharmacological intervention for prevention of AMS upon rapid ascent to high altitude and is in common practice[1]. Acetazolamide's complex mechanism of preventing altitude sickness involves renally stimulated metabolic acidosis ensuing in diuresis and increased ventilation, and supression of cerebrospinal fluid production[10]. However, acetazolamide has its side effects which include gastric distress, constipation, fatigue etc[11]. An encouraging approach is the use of intermittent hypoxic exposure (IHE) at sea level which helps in acclimatisation and reduces the incidence of AMS.

IHE can be administered using either hypobaric hypoxia or normobaric hypoxia. Hypobaric hypoxia is simulated by decreasing the barometric pressure, while normobaric hypoxia is induced by reducing the fraction of oxygen in inspired air (FIO_2). Currently, intermittent normobaric hypoxia

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training is being extensively used to improve physical fitness of an individual[12-14]. However, the study on the efficacy of intermittent normobaric hypoxia on reducing incidence of AMS and improving physical work performance on subsequent ascent to actual high altitude (hypobaric) environment is very limited. Nagasaka and Satake[15] first hypothesised that IHE in hypobaric chamber could induce pre-acclimatisation more effectively than chronic hypoxia. They exposed the subjects for consecutive days simulating 6000 m (354 mm Hg) for 5 h and 8000 m (270 mmHg) for next 1 h observed an increase in V_I and PaO_2 in hypobaric hypoxia, indicating the initiation of ventilatory acclimatisation. The training in intermittent normobaric hypoxia at sea level and its effect on AMS is very limited[16,17]. Today there is only one study that has reported the use of normobaric hypoxic exposure during sleep at sea level and its effect on AMS during subsequent exposure to hypobaric hypoxia[18]. None of the previous studies have assessed the effect of intermittent normobaric hypoxia exposure (IHE) at sea level and its effect on the incidence of AMS during acute exposure to 3500 m altitude in altitude in Indian military personnel. The objective of this study is to see the efficacy of intermittent normobaric hypoxia exposure at sea level for the prevention of prevalence of AMS during acute exposure to 3500 m altitude in Indian army soldiers.

2. METHODS

The study was conducted on 24 Indian Army volunteers. All the volunteers were male, sea level residents and non-smokers. None of the volunteers had been to high altitude within the previous 3 months. All the volunteers were medically fit. Experimental group comprised of 14 Army volunteers (age 24.71 yrs $\pm$ 3.15 yrs, height 172.36 cm $\pm$ 4.60 cm, body weight were 66.68 kg $\pm$ 9.63 kg). Control group consisted of 10 Army volunteers (age 25.90 yrs $\pm$ 4.63 yrs, height 174 cm $\pm$ 3.53 cm, body weight were 64.45 kg $\pm$ 0.08 kg). The study protocol was approved by the Institute's Ethical Committee, the volunteers were made aware of his right to withdraw from the study at any point in time without prejudice and an informed consent was taken from all the volunteers. The base line study was conducted at DIPAS, Delhi (barometric pressure 740 mm Hg) and 20 °C – 24 °C with a relative humidity range of 40 per cent – 50 per cent was maintained in the laboratory. After recording the base line data for two days, volunteers were allowed to breath 13.5 per cent O_2 (altitude - equivalent 3500 m) in normobaric hypoxia chamber for one hour (pre-hypoxic challenge). On the next four consecutive days, the volunteers were exposed at 12 per cent O_2 (altitude - equivalent 4350 m) in normobaric hypoxia chamber for four hours per day. On the fifth day, volunteers were again exposed to 13.5 per cent O_2 (altitude - equivalent 3500 m) for one hour (post –hypoxic challenge). Pulse oxygen saturation (SaO_2) level in blood and heart rate were continuously monitored during exposure. On the very next day (sixth day), the volunteers were inducted by air, within 24 hours to an altitude of 3,500 m (barometric pressure 483 mmHg), at Leh, India, the flight duration is of 55 min - 60 min. At Leh all the parameters were recorded in the morning for six successive days, the ambient room temperature was maintained between 20 °C and 25 °C (Fig. 1). The first recording of the parameters was completed early next morning (within 24 h of arrival at HA). Heart rate and oxygen saturation were recorded. Ventilatory parameters like VE, VO_2, ventilatory drive (V_T/ Ti, where Ti is the inspiratory time) were recorded with the volunteers in sitting position at both the altitudes, using breath-by-breath, open-circuit metabolic measurement system (Model K4b[2] mobile breath-by-breath metabolic system, Cosmed, Italy) calibrated with certified gases and volume standard. Venous blood samples were drawn in fasting condition at sea level and at high altitude residence (3 days and 6 days) for estimation of erythropoietin (EPO, ELISA, BIOMERICA, USA).

3. INTERMITTENT HYPOXIC EXPOSURE

Before Intermittent hypoxic exposure (IHE), pre-hypoxic challenge and post – hypoxic challenge were performed at sea level (13.5 per cent FIO_2, altitude equivalent 3500 m, Leh) in the morning after a breakfast using hypoxic air, in which hypoxic air was produced by injecting medical grade nitrogen through solenoid valve into normobaric hypoxia air chamber. During IHE exposure, hypoxic air was breathed continuously for four hours per day for four days in experimental group of volunteers in a sitting relaxed position. Hypoxic air consists of 12 per cent oxygen and balance nitrogen (12 % FIO_2, altitude - equivalent 4350 m, final SaO_2 in blood was around 87 % - 88 %). Throughout the training period, volunteers were carefully monitored. None of the volunteers presented any symptoms of mountain sickness or physical deterioration during normobaric hypoxia exposure. Control group of volunteers were breathing ambient air i.e; 21 per cent oxygen (Sea level, SaO_2 in blood was 98 % - 99 %).

4. ACUTE MOUNTAIN SICKNESS SYMPTOM SCORES

Incidence of AMS in IHE and control group of volunteers at both the sea level and high altitude locations were scored with the help of the standard Lake Louise questionnaire (LLS)[19]. Total LLS scores more than > 3 (range 0 to 15) were considered as AMS.

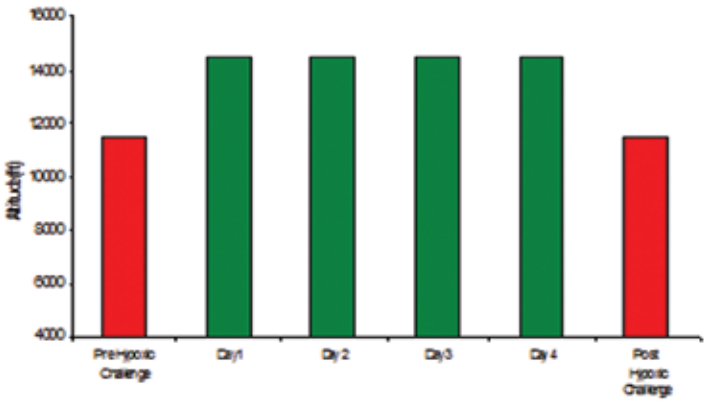

Figure 1. Study design (Intermittent normobaric hypoxic exposure at sea level followed by actual hypobaric hypoxic exposure in field condition).

5. STATISTICS

All data were presented as mean ± SD. The statistical analysis for the multiple comparison of various physiological responses within the group at different conditions has been made by the method of two-way classification of analysis of variance (ANOVA). Unpaired *t*–test was applied for comparison of various physiological responses between two groups. Probability values of <0.05 were considered as statistically significant.

6. RESULTS AND ANALYSIS

The incidence of AMS determined from LLS scoring increased from SL to high altitude on acute induction. The prevalence and severity of the symptoms of AMS was significantly less (P<0.05) in IHE treated experimental group as compared to control group on first two days of exposure at altitude. On day 1 at HA, 60 per cent of control group had symptoms of AMS while the IHE treated group showed only 5 per cent (P<0.05). On day 2 at HA, the incidence of AMS in control group declined to 40 per cent. The experimental group did not show any symptoms of AMS. On day 3 onwards no one from either group suffered from any symptoms AMS as shown in Fig. 2.

At SL, there was no differences of SaO_2 between the control and IHE treated groups (experimental: 97.93 % ± 0.27 %; control: 98 % ± 0.18 %). Pulmonary gas exchange as measured by SaO_2 was improved around 2 per cent from pre-hypoxic to post -hypoxic challenge (13.5 % FIO2). On acute exposure to 3500 m high altitude, both the groups showed statistically significant decrement of SaO_2 (P<0.05). However, the experimental group (IHE treated) showed less drop in SaO_2 (around 2 %) value on day 1 in comparison to control (experimental: 93.57 % ± 1.34 % vs control: 91.58% ± 1.80 %) (P<0.05). At high altitude, from day 2 onwards SaO_2 value increased gradually (P<0.05) in both the groups, but the experimental group maintain relatively higher value in comparison to control and maintained this trend up to day 6 (expertmental: 95.50 % ± 0.09 % on day 6 vs control: 94.50 % ± 0.75 % on day 6) as shown in Fig. 3.

Basal value of pulmonary ventilation (V_E) did not show any statistical significant difference both in IHE and control groups

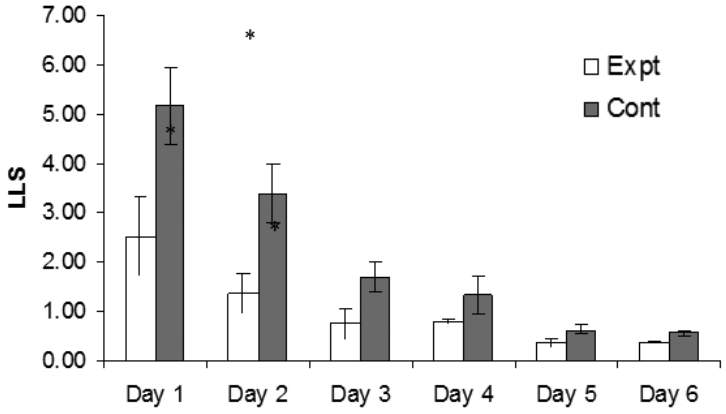

Figure 2. Symptoms of AMS score in different days at HA (3500 m), Values are mean ± SD.

*Significantly different between groups, P < 0.05.

(experimental: 9.79 % ± 1.89 %; Control: 9.54 % ± 1.51 %). On exposure to HA, both the groups showed significant increase in ventilation (P<0.05) on exposure to altitude as shown in Fig. 4. At high altitude, V_E of IHE treated group reached its maximum value on second day of induction and remained elevated on subsequent days. Whereas the control group showed a gradual rise at HA and reached its maximum by day four. The V_E values of control group was also significantly (P<0.05) lower on day 1 and day 2 in comparison to IHE treated group.

Basal oxygen consumption (VO_2) at sea level for experimental and control groups of volunteers was similar (experimental: 255.59 ± 58.35; Control: 242.4 ± 39). On induction to 3500 m altitude, experimental groups showed a significant rise in VO_2 on day 1 of exposure and thereafter it remains almost same levelas shown in Fig. 5. Whereas the control group showed a gradual rise of VO_2 at high altitude and reached its maximum value by day four. The VO_2 values of control group were significantly (P<0.05) lower on day 1 in comparison to IHE treated group.

V_T/Ti, as an index of ventilatory drive was similar in both the groups (experimental: 0.37 ± 0.08; Control: 0.38 ± 0.09) at sea level. Ventilatory drive increased significantly in both the groups at high altitude. However, IHE treated group showed significantly (P<0.05) higher value on day 1 and 2 in comparison to control group as shown in Fig. 6.

EPO values were similar at sea level in both the control and IHE treated groups. On exposure to HA (day 3), EPO value increased significantly (P<0.05) in IHE treated group in comparison to control (experimental: 23.86 ± 3.14; control 19.43 ± 2.97). From day 3 to day 6 of high altitude residency, EPO value declined in both the groupsas shown in Fig. 7.

7. DISCUSSION

The present study was carried out to assess the efficacy of intermittent normobaric hypoxia exposure at sea level on the occurrence of AMS during acute ascent to 3500m altitude in Indian soldiers. The results of this study indicated that the incidence of AMS during hypobaric hypoxia exposure to 3500 m was reduced significantly in IHE treated group. The incidence of AMS in un-acclimatised persons rapidly increases from 20 per cent to 70 per cent at the altitude between 2000 m to 3960 m. The immediate response to acute hypoxia is augmented ventilation, which is mediated through chemoreceptor to compensate the hypoxic stress[6]. Our observation on V_E at 3500 m indicates a better and fast respiratory adaptation for (IHE) treated group. This improves blood oxygenation (SaO_2) and is known to be the most effective mechanism of altitude acclimatisation during the initial days of residence at high altitude. The correlation between high level of SaO_2 and reduced acute mountain sickness (AMS) have already been reported in hypoxia condition[20]. Study also showed significantly higher level of SaO_2 in the IHE group during initial days of hypobaric hypoxia exposure at 3500 m altitude in comparison to control. Normobaric hypoxia exposure induces a comparable degree of ventilatory acclimatisation in different combinations

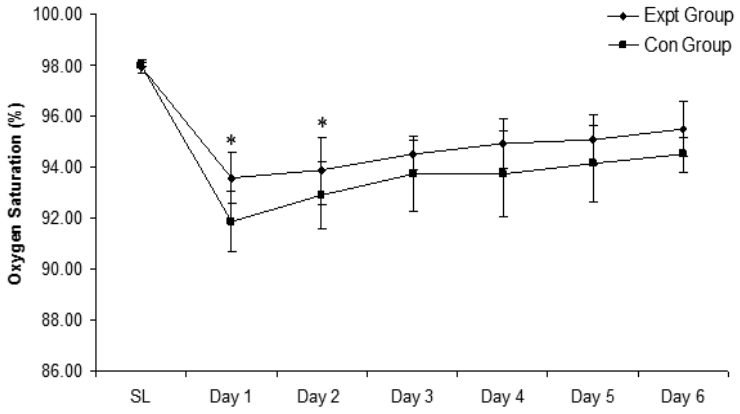

Figure 3. SaO_2 changes at sea level and different days at HA (3500 m), Values are mean ± SD. * Significantly different between groups, $P < 0.05$.

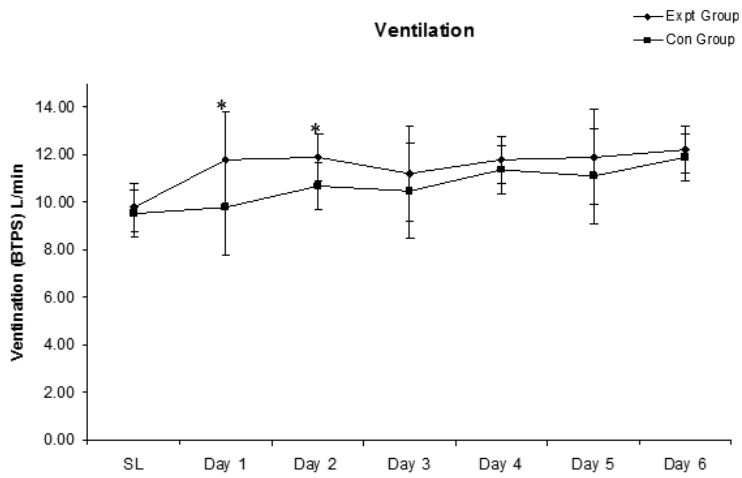

Figure 4. Ventilation (V_E) responses at sea level and different days at HA (3500 m), Values are mean ± SD. *Significantly different between groups, $P < 0.05$.

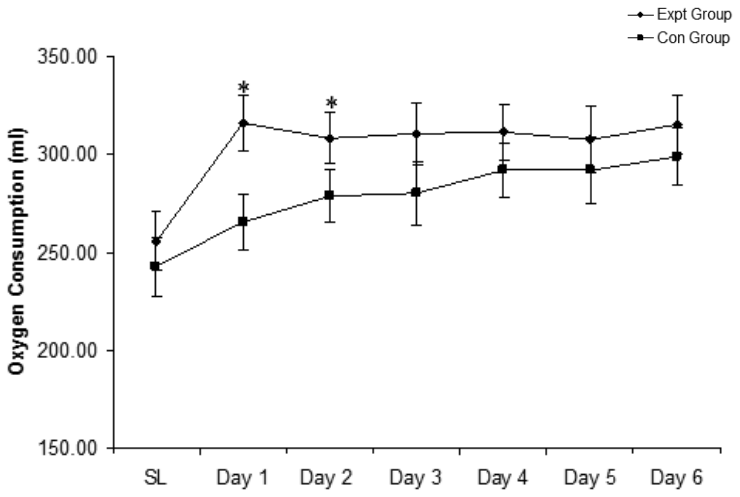

Figure 5. Oxygen consumption at sea level and different days at HA (3500 m), Values are mean ± SD. *Significantly different between groups, $P < 0.05$.

such as altitude, exposure duration and number of hypoxic exposure / sessions[21]. The studies on the effect of (IHE) at sea level and its possible outcomes on reducing the susceptibility to AMS during subsequent high altitude sojourn are very limited. Only two laboratory based studies have showed a significant reduction in the incidence and severity of AMS after IHE at sea level in laboratory based condition[17,18]. The effect of intermittent hypoxia (normobaric) and its physiological outcome during subsequent exposure to actual field condition (hypobaric hypoxia) is scanty. Schommer[22], *et al.* studied the normobaric hypoxia exposure of 14 h - 18 h in 12 per cent - 16 per cent O_2 for 70-90 min per day at the rate of 3 days per week for four weeks along with an overnight stay at 3611 m on arterial blood gases or AMS during subsequent hypobaric hypoxia residence at 4559 m. The effect of repeated normobaric hypoxia exposure in un-acclimatised sea level residents during sleep for 7.5 h in each night for seven consecutive days on acute mountain sickness and sleep during subsequent exposure to hypobaric hypoxia at 4350 m altitude showed significantly higher SaO_2 and AMS upon awakening was lower[18]. Our study is also first to report where volunteers breathed normobaric hypoxia air (12 % F_IO_2) for four hours per day for four consecutive days on acute mountain sickness at 3500 m high altitude. The results of this study indicated that normobaric hypoxia air breathing for four hours per day for four consecutive days showed the 2 per cent higher level of SaO_2 (at 12 % F_IO_2, altitude equivalent 4350 m altitude) in experimental group of volunteers. Muza[21], *et al.* in a comprehensive review recommended that an IHE exposure of altitude greater than 4000 m and daily exposure of no less than 1.5 h, repeated over a week or more are requisite to effectively develop altitude acclimatisation. Previous study from this laboratory compared the gradual ascent in four days from 2150 m to 3500 m with air induction in one hour[23]. The result showed the incidence and severity of AMS was more in air inductees in comparison to road inductees. This study also showed higher level of resting ventilation and oxygen saturation in road inductees on initial days at 3500 m altitude. Our study also showed the significantly higher resting SaO_2, V_E and also ventilatory drive (V_T/Vi) in the IHE treated group in comparison to control in initial two days at high altitude. IHE group of volunteers showed significant Increase in VO2 at high altitude is also considered as an index of altitude acclimatisation. Increase VO2 may be due to increase in ventilation as well as the changes in different biochemical indices like increase in HIF and its derivatives like EPO, HOG, NO etc which facilitates oxygen utilisation system at the cellular level. The low incidence of AMS in experimental group of volunteers at 3500 m altitude (13.5 % FIO_2, altitude - equivalent 3500 m) in IHE treated group may be due to increase

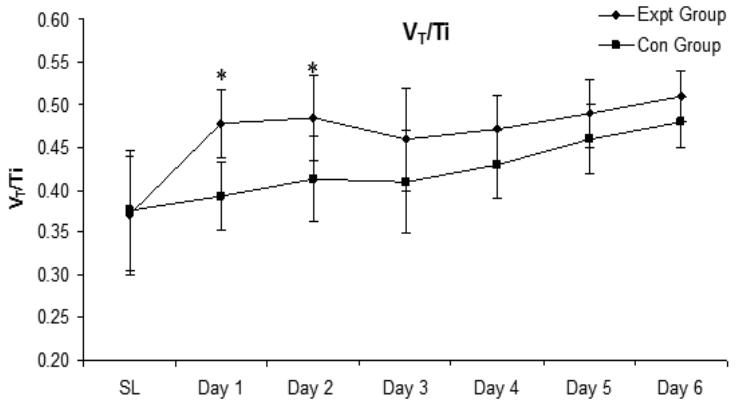

Figure 6. Response in V_T/Ti at sea level and different days at HA (3500 m), Values are mean ± SD. *Significantly different between groups, $P < 0.05$.

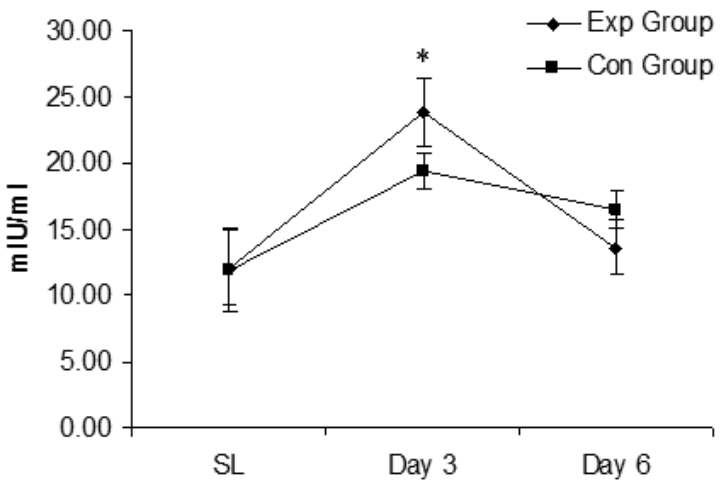

Figure 7. Changes in EPO at sea level and different days at HA (3500 m), values are mean ± SD. *Significantly different between groups, $P < 0.05$.

in chemoreceptor sensitivity in hypoxia air breathing during IHE session at higher altitude (12 % FIO_2, altitude equivalent to 4,350 m). We could not measure chemoreceptor sensitivity and this is the limitation of our study. Exposure to high altitude exhibits an increase in the breathing drive which is associated with increase in pulmonary ventilation[24]. Increase of V_T/Vi at HA is considered as an index of ventilatory drive which facilitates the ventilatory acclimatisation process[25]. Our study showed significant increase in V_T/Vi with a corresponding rise in V_E in experimental group of during initial days of high altitude exposure. The increase in V_E at HA is thought to be a result of an increased stimulation of peripheral chemoreceptor in response to the reduction in arterial oxygen content. The short term intermittent hypoxic training enhances the peripheral chemo sensitivity to hypoxia due to better respiratory adaptation and effective oxygen transport system in the tissues of IHE treated group during initial days of acclimatisation. On the contrary the control group, deprived of this gradual acclimatisation and suffered from high degree of hypoxic stress in the first few days of exposure at high altitude. They show relatively lower value of V_E, V_T/Vi as well as lower value of SaO_2. It appears that the required magnitude of hyperventilation has not been achieved immediately for control group but occurs gradually, during which period they were undergoing a higher level of hypoxic stress. In the present study showed that only 5 per cent of IHE treated group suffered from AMS whereas in the control group it was 60 per cent on first day of induction to 3500 m altitude. Hence on the basis of observation, we conclude that an intermittent normobaric hypoxia (IHE) exposure consisting of 12 per cent FIO_2 (altitude – equivalent 4350 m) for four hours per day for four consecutive days significantly reduces the incidence of AMS upon acute exposure to 3500 m altitude.

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