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Efficacy of salmeterol 50 µg and fluticasone 250 µg combination therapy for the treatment of high altitude cough: A randomized controlled trial at Everest base camp

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Efficacy of salmeterol 50 μg and fluticasone 250 μg combination therapy for the treatment of high altitude cough: A randomized controlled trial at Everest base camp

Abstract

High altitude cough (HAC) is a common problem among climbers and sojourners to mountains. There is still no evidence-based treatment for this condition, likely because the very pathophysiology of the condition is not precisely known. We studied the efficacy of salmeterol 50 mcg and fluticasone 250 mcg combination, one puff twice a day, in the treatment of HAC through a double-blind, placebo-controlled, randomized controlled trial.

At Everest Base Camp (EBC), we enrolled 52 otherwise healthy individuals with HAC seeking treatment at the EverestER, a Himalayan Rescue Association Medical Clinic, during climbing season 2010/2011 and randomized to receive either salmeterol/fluticasone combination or placebo using rotahalers. The diagnosis was one of exclusion after completion of a self-administered questionnaire and physician examination.

Forty two participants completed the trial, eighteen in treatment arm and 24 in placebo. Self-reported improvement of cough, Quality of Life assessment by a modified Leicester Cough Questionnaire (MLCQ) and clinical data were collected for analysis. Improvement of cough was assessed by Fisher exact test, MLCQ score and clinical parameters using Mann Whitney U test and Wilcoxon signed rank test. Analysis showed that combination treatment was not more effective than placebo in decreasing the severity of cough (P= 0.645). The odds ratio of significant improvement under treatment was 0.87 (95% CI 0.25-3.05). Mean MLCQ Score was 13.54±3.08 at baseline and 16.34±3.28 at follow up (P< 0.001). The difference was larger for the placebo arm (P<0.001) than the treatment arm. Improvement in cough and MLCQ score correlated with some symptoms and their severity at follow up.

We concluded that inhaled salmeterol/fluticasone combination treatment through a rotahaler is not effective in treatment of the high altitude cough in EBC.

Key Words

(High altitude cough, Randomized controlled trial, Everest base camp, modified Leicester cough questionnaire)

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Abbreviations

ACE: Angiotensin converting enzyme

AMS: Acute mountain sickness

COPD: Chronic obstructive pulmonary disease

DBP: Diastolic blood pressure

EBC: Everest base camp

FEV1: Forced expiratory volume in first second

FVC: Forced vital capacity

GERD: Gastro-esophageal reflux disease

HAC: High Altitude Cough

HACE: High altitude cerebral edema

HAPE: High altitude pulmonary edema

HPV: Hypoxic pulmonary vasoconstriction

HR: Pulse rate (Heart rate)

IQR: Interquartile range

ISRCTN: International standard randomized controlled trial number

LCQ: Leicester cough questionnaire

mmHg: millimeters of mercury

MLCQ: Modified Leicester cough questionnaire

Na+: Sodium ion

PEF: Peak expiratory flow

PND: Postnasal drip

PNDS: Postnasal drip syndrome

SBP: Systolic blood pressure

SD: Standard deviation

SpO2: Oxygen saturation

UACS: Upper airway cough syndrome

VMR: Vasomotor rhinitis

Abstract

High altitude cough (HAC) is a common problem among climbers and sojourners to mountains. There is still no evidence-based treatment for this condition, likely because the very pathophysiology of the condition is not precisely known. We studied the efficacy of salmeterol 50 mcg and fluticasone 250 mcg combination, one puff twice a day, in the treatment of HAC through a double-blind, placebo-controlled, randomized controlled trial.

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1. Introduction

1.1. Cough

Cough is a voluntary or reflexive explosive expiration that provides a normal protective mechanism for clearing the tracheobronchial tree of secretions and foreign material. It occurs as a consequence of aspiration, the inhalation of particulate matter, pathogens, accumulated secretions, postnasal drip, inflammation, and mediators associated with inflammation [1]. It is the most common symptom for which primary health care is sought for [2]. Persistent cough, in absence of other respiratory symptoms account for 10-30% of referrals to pulmonary specialists [3].

Cough commonly presents as a symptom of a disease of the respiratory tract or otherwise and rarely can present as the sole symptom. Symptomatic cough is divided into acute, sub-acute and chronic for diagnosis and management. Acute cough lasts less than 3 weeks and is commonly due to a respiratory infection, aspiration or noxious chemical or smoke inhalation. Sub-acute cough lasts 3-8 weeks and is commonly due to residual tracheo-bronchitis and bronchial hyper-responsiveness due to specific infections such as *Mycoplasma pneumonia* and *Bordetella pertussis*. It is usually a post-infective tussive syndrome. Sub-acute cough can also be caused by non-infectious factors such as gastro-esophageal reflux, aspiration, bronchial asthma and subclinical heart failure with fluid overload [4]. Chronic cough lasts more than 8 weeks and is caused by wide range of cardiopulmonary diseases. Cough variant asthma, gastro-esophageal reflux disease, nasopharyngeal drainage (upper airway cough syndrome or the postnasal drip syndrome) and use of drugs are most common causes of chronic cough in absence of x-ray changes in the lungs [2, 3].

Cough is a clue to the presence of respiratory disease. However, excess cough may lead to complications. Patients with excessive cough may also suffer from emesis, muscular pain, syncope, rib fractures, aggravation of abdominal and inguinal hernias and urinary incontinence [3].

Cough affects not only the physical but also the psychological and social facets of daily life in patients. Such effect can be measured by disease specific questionnaires which assess the overall quality of life. Quality of life in patients with cough is decreased significantly and can be measured

with cough specific quality of life questionnaires [5, 6]. Some cough specific questionnaires that have been validated are the Leicester Cough Questionnaire (LCQ) and the Cough Quality of Life Questionnaire (CQLQ) [5-7].

Even when cough is present as a troublesome symptom, is not always easy to determine the cause of cough. It is recommended to treat cough with respect to its etiology, type and severity of cough. Whenever possible, treatment of cough should be the therapy of underlying disease. On cases when a cause is not found, trial of an inhaled steroid, an inhaled beta-agonist or an inhaled anticholinergic agent is recommended. Only in severe cases of irritative and non-productive cough, suppression with a narcotic or a non-narcotic antitussive agent is recommended [2].

Acute, sub-acute and chronic cough should be investigated and etiology determined before treatment. The term unexplained cough is used for cough for which etiology is not yet known [2].

1.2. High Altitude Cough (HAC)

High Altitude

High altitude is defined by altitudes higher than 2500 meters and exposure of travelling individuals to hypobaric hypoxia. At 2500-3500 meters, acute exposure can cause decreased performance and change in sleep quality [8, 9]. Very high altitude is taken to be from 3500-5800 meters (3500-5500 meters taken by some authors [10]) and is characterized by fall in oxygen saturation below 90% with common altitude illness and marked hypoxemia during sleep and exercise [9]. Above 5800 meters altitude (5500 meters according to some authors [10]), survival cannot be maintained permanently and there is progressive physiological deterioration with marked hypoxemia at rest [9].

Approximately 30 million western state visitors sleep at altitudes 2000 meters and reach maximum altitudes of 3500 meters or higher each year. In the Everest region, 15,000 visitors each year sleep at altitudes 3000-5200 meters [10]. All these visitors start to feel a host of changes in their bodies by being at altitude. Because of the progressive decreases in partial pressure of oxygen in the air, hypoxia develops. This hypobaric hypoxia initiates other related changes such as decrease in exercise capacity,

disturbances in sleep, various neuropsychological changes, and other effects of low temperatures and high ultraviolet light penetration [9, 10]. If human physiology does not adapt to the changing needs of the altitude, people suffer from various illnesses. These illnesses are called altitude illnesses and are primarily related to the failure of so called acclimatization, a process of temporary adaptation in the high altitude environment[8].

Acclimatization is a complex series of physiologic adjustments that improve the oxygen delivery at the cellular level and improving the tolerance of tissues to hypoxia [10]. Acclimatization occurs over a short period of time. When these changes occur over decades to generations and confer advantages for life at high altitude, the process is termed 'altitude adaptation'. The main changes seen in the body physiology during acclimatization are hyperventilation, increase in red cell mass, redistribution of blood flow in the body, hemoconcentration and diuresis. Above very high altitudes exists the zone of high altitude deterioration with progressive weight loss, worsening appetite, poor sleep, and increased lethargy [9].

Failure to acclimatize at high altitude may manifest in altitude sicknesses. The most common of these sicknesses in the acute mountain sickness (AMS) which is a symptom complex of headache, gastrointestinal upset, sleep disturbance, fatigue, and dizziness in varying degrees. Severe AMS can progress to life-threatening high altitude cerebral edema (HACE), where worsening of all the signs of AMS occurs along with neurological impairment visible as ataxia and altered mental status [9, 10]. Another life-threatening disease high altitude pulmonary edema (HAPE) occurs at altitude is characterized by profound dyspnea, fatigue and cough with or without symptoms of AMS and HACE [9]. Apart from these classical altitude-related diseases, there are other conditions and diseases either exacerbated at altitude or caused by being at altitude. Among others, a common problem at sea level and low altitude regions of the world, cough, is also a common problem at high altitude.

Cough at high altitude

Dry, hacking cough is a common problem at high altitude[11]. Chronic cough is almost universal in persons spending more than few days at

extreme altitude [12-14]. Climbing and expedition journals to high and extreme altitudes are seldom complete without the mention of HAC.

HAC is also called the Khumbu cough after the famous Khumbu icefall at the base of Mt. Everest. Similar cough is also seen in other high altitude destinations around the world and can be described as high altitude bronchitis.

Causes of HAC

Exact pathophysiology of HAC has not been described though there are numerous hypotheses regarding its causation [9, 10].

At altitude, hypoxia lowers cough threshold [12, 15, 16]. Initially, in setting of hypoxia, cold and dry air of altitude was thought to cause HAC [10, 17]. Operation Everest III, a hypobaric chamber study, demonstrated an increase in cough frequency and cough receptor sensitivity with hypobaric hypoxia in a temperature and humidity controlled environment [18].

In a hypoxic environment, human respiratory physiology adapts depending on the level of hypoxia. Hyperventilation is an early physiological change in response to hypoxia. During acclimatization to high altitude, minute ventilation increases [19] resulting in increased water loss from the respiratory tract mucosa [20]. Further, the respiratory water loss is increased by the effect of exercise and hyperventilation [21, 22]. Loss of water from respiratory tract due to hyperventilation and/or exercise at altitude causes desiccation of the airway. Drying of airways can result in symptomatic cough[17].

Hypocapnia ensuing from hyperventilation at altitude is also a potent broncho-constrictor. At high altitude, both hypoxia and hypocapnia are broncho-constrictors [23]. Hyperventilation induced bronchoconstriction is also associated with epithelial cell damage, and release of biochemical mediators in humans [20]. Bronchoconstriction can also be directly caused by exercise even in healthy persons [24]. It is also a chief feature of asthma. Degree of bronchoconstriction is correlated with cough in healthy as well as asthmatic subjects [25]. At high altitude, bronchoconstriction due to various causes can be a cause for HAC.

Hypoxic pulmonary vasoconstriction (HPV) causes pulmonary artery pressures to rise. At high altitude, this rise in pulmonary artery pressure causes increased micro-vascular hydrostatic pressure at the pulmonary capillary bed. On sufficient rise of the pressure, stress failure of the vascular endothelium causes the leakage of fluid to pulmonary interstitium and then to alveoli causing high altitude pulmonary edema (HAPE) [26, 27]. Impaired trans-epithelial clearance of sodium and water is thought to play a part in the development of edema, other supposed mechanisms contributing include altitude related endothelial dysfunction and impaired release of nitric oxide, exercise and cold related rise in pulmonary vascular pressure, hypoxia related increased sympathetic drive and increased vascular permeability secondary to infections and inflammation [28]. This edema occurs in 3 stages, starting with interstitial edema, leading to alveolar wall edema and finally alveolar flooding. One of the symptoms of HAPE is cough and occurs in up to 50% of the patients suffering with HAPE [29]. Though the relation of cough to HAPE is clear, patients with HAC do not suffer from frank HAPE. But it is still not clear whether sub-clinical HAPE, probably in the interstitial phase of edema, can lead to cough. Work from cardiogenic pulmonary edema points to the role of broncho-pulmonary C-fibers in causing tachypnea and dyspnea, but cough is not a predominant symptom. In light of debated role of C-fibers in cough production, there could be other receptors stimulated by the sub-clinical edema fluid, namely rapidly adapting receptors (RARs), as shown in rabbits[16]. Though the role of RARs is also debated in cough [30], it is thought to provoke cough response from mechanical stimuli [31], which here is the sub-clinical pulmonary edema of high altitude.

Another factor at high altitude related to cough may be infections and post-infectious inflammation of the respiratory tract. In hypoxic conditions, we are prone to infections [32]. Often minor infections in high altitude areas might go undiagnosed since these areas are not always well equipped diagnostically. There are reports of green, purulent sputum associated with HAC but the common antibiotics do not seem to work [33]. In spite of this, there is still a chance that the cough could be an undiagnosed viral or bacterial condition that does not respond to the usual antibiotics recommended.

90% of all chronic cough is diagnosed to be caused by post-nasal drip syndrome, asthma, gastro-esophageal reflux disease or chronic bronchitis [34]. These are also the most frequent non-infectious causes of sub-acute cough that has not yet passed the 8 week mark [4, 35].

Postnasal drip syndrome, or the upper airway cough syndrome, results from a multiplicity of rhino-sinus conditions, among which are allergic and non-allergic rhinitis, infectious and post-infectious rhinitis and sinusitis, rhinitis due to physical or chemical irritation and other forms of rhino-sinusitis [35]. Cold air, change in barometric pressure, temperature and humidity can cause a non-allergic vasomotor rhinitis [36]. High altitude, also a cold environment with hypobaria and decreased humidity, may cause rhinitis and post-nasal drip.

Gastro-esophageal reflux disease is commonly associated condition with the development of sub-acute and chronic cough. GERD as a cause for chronic cough is reported as 5-41% in different studies[37]. This disorder can cause cough by different mechanisms, irritation of upper airways, lower airways by micro- or macro-aspiration or stimulation of esophageal-bronchial cough reflex [37]. At high altitude, prevalence of gastro-esophageal reflux disease has been found to be high [38].

Both atopic and non-atopic asthma benefit from being at altitude [39, 40] but exercise induced bronchoconstriction has been reported in ski-mountaineers [41]. Exercise in a cold environment increases exercise-induced bronchoconstriction [42]. High altitude represents an environment of physiological exertion and HAC could as well be a manifestation of the bronchoconstriction due to the time spent there.

Cough reflex and changes at high altitude

Cough is a complex reflex; though it is a protective mechanism, there are cortical influences on it. There is no evidence seen for a cough center in the brain, and cough is brought about by the regulation of breathing pattern by the respiratory center. Cough is under voluntary control, but is not inhibited in anaesthetized subjects with respiratory depression and is suppressed by antitussive drugs with minimal depression of respiration [31]. These relations have not been well understood.

Cough originates from the sites innervated by vagus nerve, including ear, respiratory tract and abdomen. In the respiratory tree, in man, cough cannot be elicited from bronchiolar and alveolar irritation. The major afferent stimulus for cough in man thus is from larynx to the segmental bronchi. In man, additionally, larynx is thought not to be the important tussigenic zone but animal studies have shown extremely mechanosensitive receptors in larynx and trachea that can be related to persistent dry cough resulting from inflammations. In bronchial tree, the receptors are more chemosensitive but repeated exposures to these chemical stimuli cause accommodation in these receptors.

These receptors can be one of the many possible present in the airways. Rapidly adapting and slow adapting receptors are myelinated Aδ and Aα fibers, while C-fibers are non-myelinated nerve fibers [31]. The so called 'cough receptors' have been proven to exist in guinea pig models and are absent in animal species that do not cough [43].The roles of rapidly adapting receptors (RARs) and C-fiber receptors present in the airways have been debated in relation to cough [30, 31, 43]. The existence of a separate 'cough receptor' that responds exquisitely to mechanical or acid stimuli has been shown in the laryngeal, tracheal and bronchial mucosa [30, 43].

Stimuli from these receptors are relayed via the vagus nerve to the *nucleus tractus solitarius*. The central mechanisms of integration of these stimuli and the corresponding brainstem response is still not completely understood [43].The cough response is a motor response, relayed through vagal and glossopharyngeal efferent nerves to the laryngeal, thoracic and abdominal muscles for a coordinated initiation of cough. Various areas in the respiratory control center adjust the different patterns of cough discharge [44].

In case of high altitude, a global depression of cerebral function is present due to hypoxia. Prolonged exposure to hypoxia decreases cough reflex [45], but exposure to hypoxia decreases cough threshold to citric acid also [18]. We do not know how individual types of receptors are affected at altitude. RARs and C-fibers respond to foreign bodies, irritants in the respiratory tract, pulmonary edema and pulmonary congestion among other causes, though the responses vary considerably between the

receptors [31]. The 'cough receptors' on the other hand primarily respond to mechanical stimuli and acid [30]. Though sub-clinical HAPE may act through RARs, or C-fibers, presence of other pathologies such as GERD and PND could cough from higher zones in the respiratory tract by stimulating the 'cough receptors' in larynx, trachea and extra-pulmonary bronchi. Dry, desiccated airway could provoke cough due to minor mechanical stimuli through 'cough receptors' too. More work is required to understand the pathophysiology of HAC and to confirm the role of these receptors. This can help treatment of HAC by providing evidence for receptor-specific therapy which then can be studied.

1.3. Problem statement

It is difficult to really provide numbers on how many people each year suffer from HAC because of the difficulty and remoteness of the expeditions. Data obtained are generally from small teams and overall situation might be somewhat different than portrayed. Also, most studies focus in the trekker, non-Nepalese population for data, there being a lack of proper data on HAC in the Nepalese climbers. Overall prevalence of cough at high altitude is not available. In many instances, distinctions are not made between various types of cough, and the numbers of pharyngitis or bronchitis are reported. In other high altitude areas of the world, in South America, high altitude bronchitis is reported to be a common cause of morbidity among climbers.

In Everest region of Nepal, prevalence of HAC has been reported in literature to be 12%[46] to 42%[11] depending on the resource consulted. At EverestER medical clinic at 5300 meters, HAC has been a leading cause for seeking medical care for last 10 years[47]. There are still at EBC a lot of climbers, especially Sherpas, who do not turn up at the clinic even though they have HAC. We also do not have the data on trekker population who reach very high altitudes of up to 5500 meters in the Everest region of Nepal and number in about 15,000 per year only in this area [10].

In addition to this, severe HAC results in failed expeditions. This is a big economic burden for the climbers. On an average, a non-Nepalese climber pays a total of 40,000$ to 100,000$ for climbing once at peak season at Mt Everest. Of this cost, 11,000$ is the cost of the permit to be paid to the

government of Nepal to climb, the rest depends on the level of logistics and support an expedition team provides [48]. For a Nepalese Sherpa, this cost is 75,000 Nepali Rupees during the spring season, with a provision for waiving from the government. The cost for a full set of good quality equipment for summiting Mount Everest is calculated to be around 8,000$. Rest of the cost depends on the quality of individual expedition base camps and the quality of guides available for the climbers [48].

Severe HAC at basecamp or broken rib due to HAC causes failed expeditions and loss of the thousands of dollars per individual climber. For a Nepalese Sherpa, inability to climb further due to HAC costs the aforementioned costs of permit and equipment as well as the loss of salary and bonus totaling in a best case scenario from 2,000$ to 6,000$[49] if they had stayed healthy and completed their climb of the summit.

1.4. A review of treatment options in HAC

HAC develops typically as a severe, paroxysmal hacking cough, most commonly non-productive, but with occasional patient complaining productive nature. The cough typically gets worse with climbing higher into the mountain and gets better on climbing down to lower altitudes, which is the only way for severe cough patients to bet any form of improvement. Even after descent, the HAC persists typically for more than 6-8 weeks, thus falling into the category of sub-acute or chronic cough. At EverestER, altitude physicians have experienced HAC patients with intercostal muscle strains, probable rib fractures (absence of x-ray facilities at EBC for confirmation), blood streaked phlegm in occasional patient and a highly affected quality of life, not to mention loss of sleep for self and others during night time paroxysms of coughing.
As such, over the years, an effective treatment for HAC has remained elusive. High altitude physicians have used many forms of treatment in HAC. The forms of treatment tried generally fall under the categories general measures that are not specific to cough; use of antitussive agents; use of antibiotics; and treatment of conditions potentially causing cough.

General measures and over the counter preparations

Use of masks, balaclavas or silk scarfs while climbing to retain the respiratory moisture and maintenance of hydration are advocated as general measures [9, 10]. Forced hydration is recommended to help

maintain the water balance, but it is not a treatment targeted specifically to respiratory mucosa. Use of masks or to retain respiratory moisture is also recommended to all climbers at altitude and is mostly for prevention. Symptomatic treatment can be tried with steam inhalation, hard candies, throat lozenges, different cough syrups and preparations [9]; though they have not been found effective in HAC. Treatment with over the counter preparations like guaiaphenesin, mucolytics, anti-histamine decongestant combination preparations, antihistamines alone and over the counter bronchodilator have not shown quality evidence in treatment of cough and have unknown efficacy in treatment of HAC [50].
Oxygen therapy to reverse hypoxia, thereby reversing the physiological changes can be hypothesized to work in HAC. Oxygen is the first form of therapy for severe and life threatening altitude illnesses, high altitude pulmonary and cerebral edema [51]. But HAC is not associated with desaturation and patients generally do worse after inhaling oxygen from canisters as the bottled oxygen lacks moisture and causes further drying of the respiratory tract.

Antibiotic treatment in HAC

Presence of purulent sputum with HAC leads to frequent trial of antibiotics to treat a possible infection. From personal experiences, for treatment of respiratory infections in Nepalese mountains trekkers are usually prescribed azithromycin from their general practitioners to be used during any doubts of infections in settings where health care is not available easily. It is not unusual to find a patient with cough self-treated with antibiotic regimen multiple times, to turn up at EverestER with the cough still not treated and with a spectrum of added complications due to side effects of the drugs used. In absence of other signs of infection; high temperature, respiratory examination findings suggestive of infection, antibiotics are not recommended in HAC [10].

Antitussive treatment

Codeine is a centrally acting opioid antitussive commonly used in treatment of cough. It is used in severe cases of HAC when other measures do not bring about an improvement in cough severity, often combined with descent of patient to a lower altitude. Two studies, one of them a double-blinded, stratified, placebo-controlled, parallel group research failed to show a difference between codeine and placebo in the

treatment of cough associated with acute upper respiratory tract infections[4]. Non-opioid antitussive, like dextromethorphan, are thought to have limited efficacy (less than 20% cough suppression) also have shown mixed results in experimental studies [52]. Overall, centrally acting antitussives have shown a marginally superior benefit over placebo in improving cough status in patients.

Though antitussives might improve cough, they are not without their costs. Codeine causes respiratory depression has been prohibited to be used in children under 12 years and in patients above 12 with respiratory function impairment [53]. It also causes drowsiness (>10%), paradoxical nervous system stimulation, dizziness and confusion in up to 10 % patients taking the drug. Dextromethorphan also causes dizziness, drowsiness and confusion as common side effects. A climber in hypoxic environment with a physiological respiratory functional impairment is put in a higher risk when s/he has to make decisions at every step of the climb that are important to safety of self and others on the mountain. This makes it imperative, especially in a high risk environment of high altitude, to find safer alternatives in treatment of HAC.

Treatment of causal factor/ related condition

Problem with specific treatment for HAC is that the pathophysiology is not established. Literature review has suggested sub-clinical HAPE, GERD, postnasal drip syndrome, bronchoconstriction and asthma and post-infectious cough as potentially treatable conditions probably resulting in HAC.

Sub-clinical HAPE as a pathophysiological basis for HAC would imply HAPE prevention treatment could have a role in its treatment. Salmeterol, a beta-agonist, is used for HAPE prevention for its action in the pulmonary Na+ channels that prevents the stress failure of the pulmonary blood- alveolar barrier and helps to keep fluid out of the alveoli [54]. Dexamethasone, by modifying various physiological processes has also been found to prevent increase in pulmonary artery pressure, thereby significantly decreasing the precipitation of HAPE in HAPE-susceptible subjects [55]. Fluticasone, though not studied specifically in HAPE, is also a steroid and could have similar beneficial effects in HAPE prevention.

Hyperventilation/hypocapnia related bronchoconstriction are reversed by beta-agonists [56]. Considering HAC to be an otherwise undetected form

of exercise-induced broncho-constriction [41] or a form of previously unidentified cold or exercise induced asthma, a combination treatment of a beta-agonist and a steroid would relieve the broncho-constriction and associated inflammation, thereby improving HAC.

Post-infectious cough is common cause of sub-acute coughs and occur after bacterial or viral upper and lower respiratory tract infections. Though the cause of infection is no more, inflammation of the airway and subsequent bronchoconstriction are responsible for cough in this scenario. For this reason, anti-inflammatory and bronchodilator drugs would be in a position to reverse cough. Steroid [57] and beta-agonist drugs are in pole position to reverse these processes.

Since vasomotor rhinitis is common in cold environments and as such in very high altitudes, reversal of rhinitis or its prevention could be a way to treat HAC. Anti-histamines and steroids are used commonly to treat VMR. Studies with fluticasone have shown that it is superior to placebo in treatment of VMR [58].

Gastro-esophageal reflux disease and its extra-esophageal manifestations are treatable causes of cough. Proton-pump inhibitors are the most effective form of medical treatment for GERD [59]. Treatment of GERD would rectify the effect of micro and macro aspirations as well as laryngo-pharyngeal reflux and thus improve or treat cough.

A combination treatment of steroid and beta agonist was studied in patients with persistent dry cough and found effective [60]. Steroids are used in treatment in low altitude for unexplained, idiopathic chronic cough. Fluticasone has been found effective in reduction of cough in non-smoking previously healthy adults [61].

2. Rationale and Objectives

2.1. Rationale

Anecdotally, high altitude physicians working at EverestER medical clinic and other high altitude health posts around the world have found the combination of steroids and beta-agonists to be effective in treatment of HAC [47]. Steroid, in this case fluticasone, can be argued to prevent HAPE, stop inflammatory processes related to asthma and infection, treat vasomotor rhinitis and PND. Beta-agonist, here salmeterol, would also prevent HAPE and reverse bronchoconstriction. Together, a combination

treatment of salmeterol/fluticasone can be argued to improve significantly or treat significantly higher number of patients with HAC in comparison to placebo treatment. If the combination treatment of fluticasone and salmeterol is found effective in treating HAC, it would simultaneously rule out the role of dry air, respiratory loss of water, active infection and gastro-esophageal reflux disease.

On the probable scenario that the drug combination has a significantly higher efficacy in improving HAC, then we could make a case for the abovementioned conditions. A follow up research with individual drugs would reveal if there is any difference between the individual components that are quite different in the pharmacological activity. Should there be a difference, a theory on pathophysiology of HAC can be generated and tested based on such results.

2.2. Objectives

The principle objective of this study was to examine whether anecdotally successful treatment regimen of salmeterol/fluticasone is better than placebo in improving self-reported cough status in HAC.

The secondary objectives of this study were:

1. To assess quality of life in patients of HAC with modified Leicester cough questionnaire (MLCQ) and to compare the change in the quality of life between treatment arms.
2. To describe associated clinical characteristics and pulmonary functions of HAC and compare between arms the effects of treatment on these variables. Pulse rate (HR), oxygen saturation (SpO2), systolic and diastolic blood pressure (SBP and DBP), peak expiratory flow (PEF) and forced expiratory volume at first second (FEV1) were to be assessed.
3. To assess role of exercise in HAC.
4. To describe symptoms related to HAC in terms of severity and find a relation between symptom severity and improvement in cough.

3. Methods

3.1. Design and patients

The study was a single-center, randomized, double-blind, placebo-controlled trial to test the efficacy of salmeterol 50 mcg and fluticasone 250 mcg combination, one puff twice a day regimen in the treatment of HAC. Rotahalers, simple dry powder inhaler devices, were used to deliver treatment combination or placebo. Enrollment took place in the months of March, April and May in 2010 and 2011 at the Everest base camp (EBC, 5300 meters) in Nepal.

Mountaineers, as they ascended to base camp, were made aware of the study by means of recruitment posters in the lodges that provided accommodation in the villages along the way to the Everest Base Camp and also by requests for volunteers at the daily altitude education talks given at the Himalayan Rescue Association post in Pheriche. Interested mountaineers were given adequate explanation regarding the study again by the EverestER doctors and asked if they would like to participate. Study staff ensured that participants did not meet any of the exclusion criteria. Participants who provided informed consent were assigned a study number and requested to fill out a baseline modified Leicester Cough Questionnaire (see attached). They had their blood pressure, pulse, peak expiratory flow, FEV1, O2 saturation measured and lung and heart auscultation carried out. Participants then received pre-randomized numbered medication packages along with rotahalers with either combination of inhaled salmeterol 50 mcg and fluticasone 250 mcg or placebo. The medication packages were pre-randomized during production at the pharmaceutical company. The rotahalers had a 14 day twice-a-day dosing supply of drug capsules. The randomization numbers of the corresponding packages were noted.

The rotahaler is a simple device (also called DPhaler) for dry powder inhalation, used together with drugs packaged in capsules, called rotacapsules or rotacaps. Rotahalers are simple to use with dry powder inhaler delivery mechanism. They are breath actuated, portable, small, without need for propellants and can be operated with less patient coordination [62]. The participants were given uniform training on the use of the rotahalers by the corresponding author and other study

administrators, all of whom were high altitude physicians involved in patient care at the EverestER.

Between days 7-14, the subjects were re-assessed using the same parameters and the modified LCQ. Unused medication was collected and remaining pill count was noted for all participants. This was then disposed of according to local regulations.

Two sealed master lists of the randomization code were held by the manufacturer, and an independent clinician at the Nepal International Clinic in Kathmandu.

3.2. Inclusion and Exclusion criteria

The inclusion criteria for the study subjects were otherwise healthy men or women; age 18-65 years; staying in EBC (5,350 meters) or higher for 2 weeks before enrollment, suffering from HAC. Signed informed consent form was essential to participate in the study.

Exclusion criteria were other diagnoses causing cough (e.g. probable viral or bacterial upper and lower respiratory tract infections, HAPE); unwillingness to comply with study treatment, contraindications for use of the drugs under study; use of beta-agonists, steroid inhalers, steroid nasal sprays or oral steroids use in the previous 2 weeks.

3.3. Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki. We obtained ethical clearance from Nepal Health Research Council and Oxford Tropical Research Ethics Committee before the start of research. Ethical clearance from Ludwig Maximilian University was obtained during the PhD schedule of first author. Written informed consent was obtained from all participants at enrollment. The trial was duly registered at the international standard randomized clinical trial registry (ISRCTN: 76835758).

3.4. Case definition

HAC was defined as persistent, sometimes paroxysmal cough of more than 1 day duration that disturbs sleep or daily activity or both at high altitude. It could be dry or productive but was not associated with fever, chills, shortness of breath or desaturation < 75 % at EBC (5300 m) and was diagnosed by high altitude physicians working at the EverestER.

For the diagnosis, clinical history and examination was completed by the physicians. During examination, auscultation of heart and lungs was carried out for all participants. Only participants with unremarkable findings on auscultation of heart and lungs along with the characters mentioned in the case definition were explained about the research procedure and invited to take a part in the study.

3.5. Instruments

3.5.1. Self-reported improvement in cough at follow-up

The self-reported improvement in cough was assessed at follow up. The response reported was a Likert scale with 5 levels of improvement in cough. The levels were coded 1-5 respectively for 'No Improvement', 'Improved a bit', 'Improved moderately', 'Improved greatly', and 'Completely resolved, No cough!'

Cough is a difficult entity to measure. As a symptom, it can be measured in various dimensions. Objective and subjective measures are both used in cough reporting. Cough counter devices and cough threshold testing are objective measures. Self-reported cough, visual analog scale and cough specific questionnaires are subjective measures [7] and are regularly used in researches of cough.

3.5.2. Modified Leicester Cough Questionnaire (MLCQ)

Leicester cough questionnaire (LCQ) is a valid, reliable tool to assess cough specific quality of life and is commonly used in cough research. LCQ was devised to assess quality of life in patients with cough. It has been validated across different settings and respiratory conditions for cough [5, 63]. The LCQ has 19 items belonging to the categories physical, psychological and social effects of cough in the patient under treatment or observation. Each category is defined as a domain. The physical domain has 8 questionnaire items, psychological domain has 7 questionnaire items and the social domain has 4 questionnaire items. The questionnaire is self-reported by the patients. On completion of the questionnaire, score is calculated from the domains, and the domain scores are added to calculate the LCQ score, which gives the idea of the quality of life in a patient.
Domain score= Total Domain Score/Number of items in the domain
LCQ Score = Physical Domain Score + Psychological Domain Score + Social Domain Score

Thus the domain scores can range from 1-7 and the LCQ score can range from 3-21.

LCQ was modified by experts in altitude medicine for use in the mountaineering population. Modified LCQ used 18 of 19 original items of the LCQ [5]. One item of the psychological domain was dropped and one question added to the physical domain. Modified Leicester cough questionnaire (MLCQ) contained 19 questions, each item a Likert scale item with possible scores from 1 to 7. 1 was the least quality of life and 7 the best quality of life possible for each question.

MLCQ consisted of three domains viz. physical, psychological and social as the parent questionnaire. The physical domain consisted of 9 questions, psychological domain 6 questions and social domain 4 questions. Participants completed the Modified LCQ at baseline and follow up. On completion of the MLCQ, scores were calculated similar to the LCQ. Domain scores were calculated and added together to get the MLCQ score.

3.5.3. Relation of HAC to exercise

HAC is still a cough of unexplained etiology. High altitude is an environment of constant hypoxic strain to human body and physiology. It is known that exercise can cause bronchoconstriction and cough in normal subjects [24]. It is not known whether exercise-induced bronchoconstriction plays a role in development of HAC. We explored the relation of HAC to exercise as 3 possibilities, a cough brought on by exercise, a cough made worse by exercise and a cough with no relation to exercise. The responses from participants were collected at baseline and follow up.

3.5.4. Symptom severity checklist

A 14 symptom checklist was developed by altitude medicine experts for use in this study to assess severity of symptoms of HAC. A 14 symptom checklist was developed by experienced altitude physicians to assess the presence and severity of various symptoms that might be associated with HAC, especially in the light of the unexplained pathophysiology of HAC. Symptoms assessed were related to the severity of cough or gastro-esophageal reflux and postnasal drip.

Symptoms related to cough severity

Symptoms ‘retching and vomiting while coughing’, ‘cough with eating’, ‘cough with certain foods’, ‘cough while getting out of bed in the morning’, ‘cough brought on by speaking or singing’, ‘cough more while awake than asleep’ and ‘chest tightness or wheeze when coughing’ assessed direct impact of cough on daily life. Wheezing is a symptom of asthma.

Symptoms related to gastro-esophageal reflux and postnasal drip

These are hypothesized pathophysiological factors for HAC. The symptoms included ‘hoarseness’, ‘heartburn, indigestion or stomach acid’, ‘tickle or lump in throat’, ‘strange taste in mouth’, ‘clearing throat’, ‘post nasal drip’. ‘Cough on lying down or bending over’ assessed cough severity as well as gastro-esophageal reflux symptom, but was pooled with the gastro-esophageal reflux symptomatology[64].

3.5.5. Clinical data

Participants went through a medical examination at the EverestER, by high altitude physicians before being diagnosed as HAC. Lung and heart auscultation were performed while taking a note of basic clinical parameters. Pulse rate, blood pressure and oxygen saturation were recorded both at baseline and follow up. Pulse rate (HR) was measured in in beats per minute, oxygen saturation (SpO2) in percentage, systolic and diastolic blood pressure (SBP and DBP) in mmHg. The treatment regimen used in the study has effects on the general clinical parameters. Salmeterol, a beta-agonist, increases heart rate [65] which can be explored at post-treatment phase in contrast to placebo. Similarly, it also has effect in decreasing diastolic blood pressure [66, 67]. Salmeterol/fluticasone combination was shown in one study not to affect oxygen saturation after inhalation for up to 720 minutes in patients with chronic obstructive pulmonary disease (COPD) [68], whether same results will be seen at high altitude remains to be seen.

High altitude brings about a decrease in FVC, increase in PEF and no change in FEV1 [23, 29, 69]. Salmeterol is an effective bronchodilator and improves FEV1 and PEF in asthmatics [70]. To measure the changes in the pulmonary function at altitude, PEF and FEV1 were chosen to be studied at baseline and follow up. Measurement of PEF and FEV1 would also reflect the degree of bronchoconstriction in the study arms at baseline and the difference brought by intervention at follow up. PEF was

measured in liters/second and FEV1 in liters using Microplus spirometer in 2010 and Jaeger Spiropro spirometer in 2011.

3.5.6. Altitude of occurrence of HAC

Altitude related cough, studied earlier by Mason, is thought generally to occur in two different forms. One type, occurring over 5000-6000 meters is hypothesized to be related with the sub-clinical HAPE and the second type, occurring below 5000 meters altitude hypothesized to be more commonly associated with airway mucosal trauma and infections [29]. We asked the participants to report at which altitude HAC occurred. The responses were reported in 6 altitude ranges; 1000-1999 meters, 2000-2999 meters, 3000-3999 meters, 4000-4999 meters, 5000-5999 meters and 6000 meters or higher. The altitude of EBC fell in the third range of 5000-5999 meters.

3.5.7. Pill count

28 rotahaler capsules were in each medication packaging the participants received at enrollment. A count of the remaining rotahaler capsules was recorded at follow up visit, as a proxy measure for compliance to treatment.

3.5.8. Demographic Information

We collected information on age, gender and nationality as well as type of expedition, time taken to reach very high altitude, time of acclimatization before enrollment, previous illnesses, current treatments and allergies. For better characterization of climbing population and understanding of possible background variables in relation to the development of HAC, these background variables were useful.

- Month of arrival at EBC: Climbing season at Everest is just a small window from the end of April to end of May. Arrival earlier or later might influence level of acclimatization at 5300 meters at EBC.

- Date of arrival and date of enrollment: These two dates would make it possible to calculate the time spent in the altitude of base camp or above, as a part of the inclusion/exclusion criteria.

- Number of nights taken from Lukla to EBC: From Lukla at 2800 m to Everest base camp at 5300 meters, it is a 2500 meters vertical ascent. According to UIAA, the international union of mountaineering federation, the recommended daily vertical ascent to be travelled at high altitude is

300-500 meters, and every 900-1000 meters to be taken as an acclimatization day[71]. This would come about to be 11 days with 300 meters/day calculation and 8 days with 500 meters/day calculation. Lesser number of days would point to incomplete acclimatization as well as higher levels of fatigue.

It is not clear how this rule applies to the high altitude residents, the Nepalese population group reflected in this study, as their physiological changes are those reflecting adaptation to high altitude and not acclimatization.

Association to the number of nights taken by a climber to reach EBC from Lukla might point out associations with the level of acclimatization profile and the development of HAC.

- Independent climber or climber in a commercial expedition: Independent climbers are under much more physical stress during climbing, especially in Everest than their colleagues in a commercial expedition team. The independent climber carries all his loads to the higher camps and sets his own camps at high and extreme altitudes whereas in a commercial expedition, there is a group of helping climbers, mainly Sherpas in Nepal, who carry the loads to higher camps and set up camping spaces. Being an independent climber is a proxy to increased physical stress. In terms of Nepalese Sherpas, this rather would not apply as they all work for commercial expeditions.

- Use of acetazolamide during trekking to EBC: Acetazolamide accelerates the process of acclimatization and is used for treatment of acute mountain sickness. Association to acetazolamide would associate HAC to acclimatization related disorders.

- Breathlessness with HAC: Breathlessness is a common symptom at altitude after any form of exercise. But breathlessness disproportionate to the level of exercise is an early symptom for high altitude pulmonary edema. A paroxysm of HAC also could leave the patient breathless for minutes after coughing. Similarly, breathlessness could also be a part of ongoing lower respiratory tract infection or inflammation. So a high proportion of breathlessness reported during HAC would warrant further examination of the variable.

- Long-term illnesses: Probable participants with long term respiratory system disease directly causing cough were excluded from study.

- Patient on any regular long term treatment: Patients on regular long term medicines that could give rise to or that could interfere with the assessment of HAC were screened by the question. Beta-agonists or steroid treatments fell under exclusion criteria. Similarly, ACE-inhibitors can be a cause for cough itself.

- Presence of allergies: This variable was used to identify presence of allergies in patients with HAC. Presence of allergies in significant amount of participant points to its association with HAC which can be explored in future studies. Presence of allergies could be a pointer to a possible association between airway hypersensitivity and HAC.

- Age: Mountaineering population is principally an adult population, mostly healthy and fit. But recent mountaineering demography points to the fact that older people are climbing mountains more. A possible difference between treatment arms could make the results biased.

- Gender: Males outnumber females in climbing, but there is no data on whether HAC is affected by gender, and if there is any association, it might affect the end result in the study.

- Nationality: Nepalese Sherpas are the local population of the Everest region and are in the mountain in a regular basis and have a genetically favorable propensity to function at high altitude. Similarly, having worked at the same environment for years, they could develop a different attitude to HAC, a disease that affects their functionality at high altitude but gradually diminishes and is cures after weeks or months of returning to their lower altitude of residence. This could bring about the differences in the MLCQ reporting compared to non-Nepalese nationals.

  Oxygen saturation, mean blood pressures and heart rate for a population adapted to live in high altitude is different to that of a non-resident of high altitude. Standard normal values for spirometry in Nepalese population are not established, but are decidedly much lower than the standard normal values for the European or American population. This could bring about a bias in the comparison of respiratory function measurements.

3.6. Outcome variables

3.6.1. Primary and Secondary Outcomes

Improvement in cough was the primary outcome of this study. Secondary outcome measures were MLCQ score for quality of life assessment, assessment of symptom checklist, HR, SpO2, SBP, DBP, mean arterial pressure (MAP), PEF and FEV1.

3.6.2. Improvement in Cough

Improvement in cough was primary outcome measure of this study; self-reported by participant at follow up visit in a 5 point scale (described in detail in 3.4.1). Improvement in cough was reported only at follow up. The outcome measure was reported and compared between treatment and placebo arms.

The responses were grouped into dichotomous variable for analysis, with scale values 4 and 5 reflecting respectively greatly improved cough and completely resolved cough considered as significant improvement in cough. Scale values 1-3 (no improvement, improved a bit and improved moderately) were considered non-significant improvement in HAC. Inference of significant and non-significant outcome was determined in placebo and treatment arm of the study, and the results reported. Comparison between arms was done at follow up and any difference tested statistically.

3.6.3. MLCQ score

The domain scores were calculated as (sum of item scores/number of items in the domain) with a range 1-7. MLCQ score was calculated as the sum of domain scores (range 3-21) [5]. MLCQ score was calculated for both arms at two points of study, baseline and follow up. The change in MLCQ score from baseline to follow up was calculated and compared across treatment arms. The change in domain scores were also reported and compared between arms. For each domain, at baseline and at follow up, reporting and comparison between groups was done for each questionnaire item.

Additionally, MLCQ scores were compared between Nepalese and non-Nepalese respondents of the study to check the consistency of response across nationalities.

Cronbach's alpha was calculated at baseline and at follow up as a reliability marker for the questionnaire. It is the statistical measure of internal consistency, it shows that all the items in a questionnaire like MLCQ are measuring the same thing and are correlated to each-other [72]. A measure of "> .9 – Excellent, > .8 – Good, > .7 – Acceptable, > .6 – Questionable, > .5 – Poor, and < .5 – Unacceptable" is generally regarded as the rule of thumb in Cronbach's alpha values [73].

3.6.4. Relation of HAC to exercise

Frequency of relation of cough to exercise was explored at baseline and explained in the total population. Comparisons were made between treatment arms with and distribution explained also by nationality. At follow up, the distribution of frequencies was explained and placebo arm compared to treatment arm to explore any differences.

3.6.5. Clinical variables

Oxygen saturation (SpO2) was measured in percentage, systolic and diastolic blood pressure (SBP and DBP) in mmHg, peak expiratory flow (PEF) in liters/second and forced expiratory volume in 1 second (FEV1) in liters. The variables were reported for each arm and compared at baseline and follow up between the study arms. Change in the variables from baseline to follow up was calculated and compared between the treatment arms.

3.6.6. Symptom severity checklist

The symptom checklist was measured in a scale 0-5, 0 denoting no problem at all and 5 denoting severe problem with the listed symptom. All 14 symptoms were explored for differences between study arms. Reporting of severity and comparison between arms was done at baseline and follow up. Additionally, change in severity from baseline levels was calculated for each symptom. The change was described across study arms and compared. The change in symptom severity was correlated with improvement in cough at follow up and change in MLCQ score in each arm at follow up.

3.6.7. Compliance to treatment

This was seen by looking at pill count on follow up. Patients were asked to return with the packaging of the rotahaler capsules and remainder were counted, noted and collected for disposal. At follow up, pill count was compared between treatment arms.

3.7. Power calculations and statistical analysis

3.7.1. Power calculation:

Power calculation for the study was done based on the primary endpoint "improvement of cough". Fisher exact test was used to test the difference among study arms. The assumptions were made for 70% patients in treatment arm to have a "Significant Improvement of cough" and 20% in the placebo group for the same result. On completion of 2 years of study period in Everest base camp, a total of 52 patients could be enrolled, with valid response to the primary outcome question reported by 40 participants at follow up. Power of 0.91 was reached during the study with 18 participants in treatment arm and 22 in placebo arm for achieving type 1 error probability rate 0.05 to prove significant difference between treatment and placebo groups.

3.7.2. Statistical Analyses:

Normally distributed values were presented as mean ± standard deviation (SD), non-normally distributed values as median, first and third quartile (Q1–Q3). Categorical data was presented as frequency and percentage. Fisher exact test and odd's ratio were used to investigate primary outcome 'Improvement in Cough'. Mann-Whitney U test and Wilcoxon Signed Ranks test were used to investigate differences between placebo and treatment and between enrollment and follow up measurement values for MLCQ and clinical variables. Correlation of improvement in cough at follow up and change in MLCQ score with change in symptom severity at follow up analyzed with Spearman's rank correlation co-efficient.

All the data was analyzed with the help of SPSS 17.0 after initial documentation on paper.

4. Results

4.1. Characteristics of Participants

52 subjects were recruited at the Everest Base Camp Clinic in 2010 and 2011 April-May spring climbing seasons. Only 3 (5.77%) enrollees were independent climbers, the rest being associated with commercial expedition groups. 37 (71%) arrived in the base camp during the month of April, 12 (23.1%) in March and 1 (1.9%) in May during both years of the

study. There was no difference between treatment and placebo arms in terms of month of arrival to EBC (P= 0.858).

46 (88.46%) males and 6 (11.54%) females were enrolled, 39 (75%) were Nepalese and 13 (25%) non-Nepalese. On comparing the placebo arm with the treatment arm, there was no difference in terms of gender (P= 1) and nationality (P= 1).

42 were successfully followed up, 6 enrollees were lost to follow up and 4 dropped out of the study. The general characteristics of the patients with HAC who were enrolled for the study are shown in the table 1.

Table 4-1 Baseline characteristics of study participants

Age (in years)		34.42±8.66
Sex	Male	46 (88.46)
	Female	6 (11.54)
No. of nights from Lukla to EBC[a]		6.10±3.81
With Allergies		0(0)
Drugs at the time of study		10 (19.23)
Using Acetazolamide		1 (1.92)
Chronic illness		3 (5.77)
Without Breathlessness		31 (59.62)
Pulse Rate (per minute)		82.37±15.48
Systolic BP (mmHg)[b]		133.43±14.99
Diastolic BP (mmHg)[b]		86.20±12.51
Mean Arterial Pressure (mmHg)[b]		101.94±12.28
SpO2 (%)		83.06±3.84
FEV1 (liters)[b]		3.62±1.01
PEF (liters/second)		8.79±2.77
Notes: Data are Mean±SD or n (%). EBC= Everest Base Camp, BP=Blood Pressure, mmHg= millimeters of mercury, SpO2= Oxygen Saturation, FEV1= Forced Expiratory Volume in 1st second, PEF= Peak Expiratory Flow. [a] N=41, [b] N=51		

Age

Mean age of the baseline population was 34.42±8.66 years. There was no difference between placebo and treatment group in mean age (Z= -0.248, P= 0.804). The Nepalese population was much younger (mean age 32.39±5.78 years) in comparison to the non-Nepalese population (mean age 41.00± 12.88 years). The difference in age according to nationality

was significant (Z= -2.02, P= 0.043). Age was not different significantly in comparison of the male and female participants of the study.

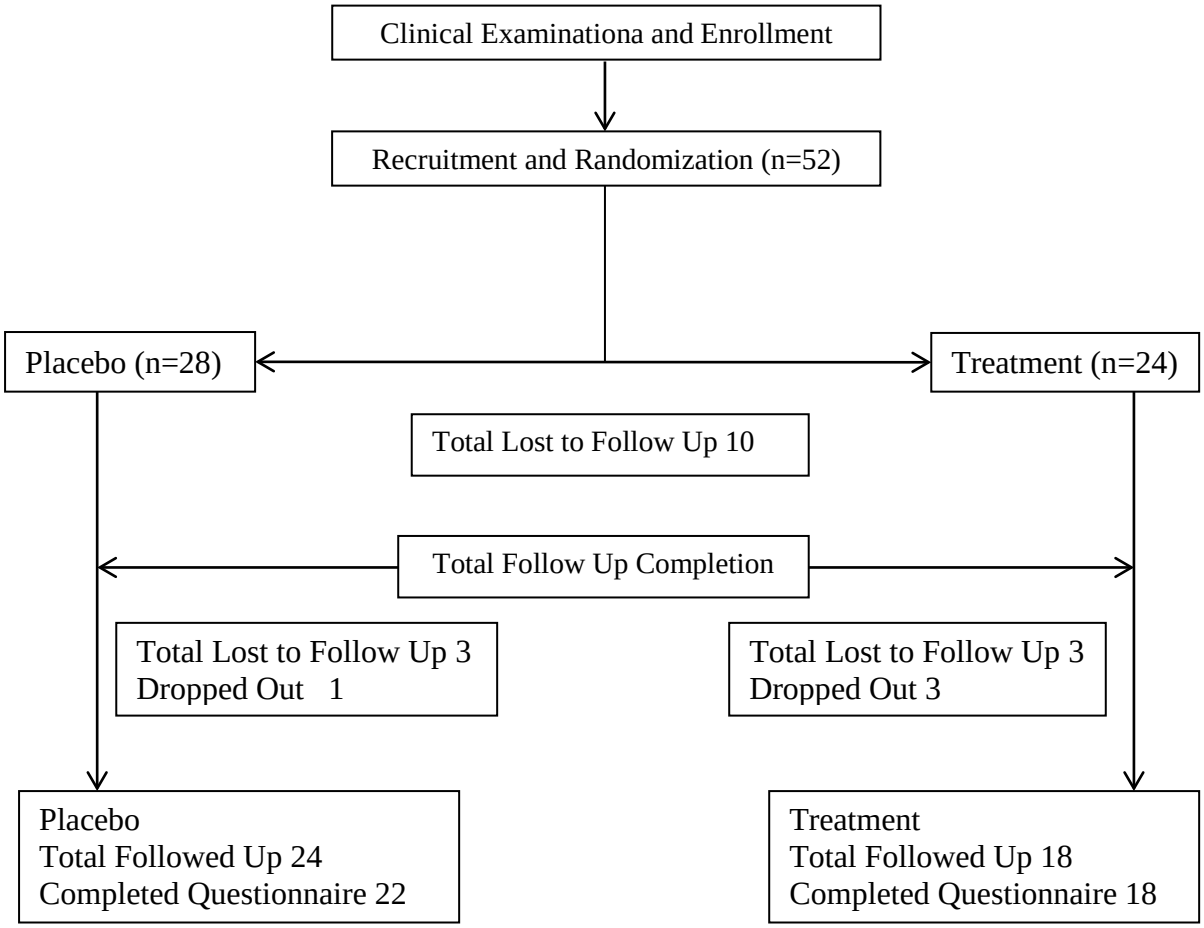

Figure 4-1: Flow diagram of HAC study

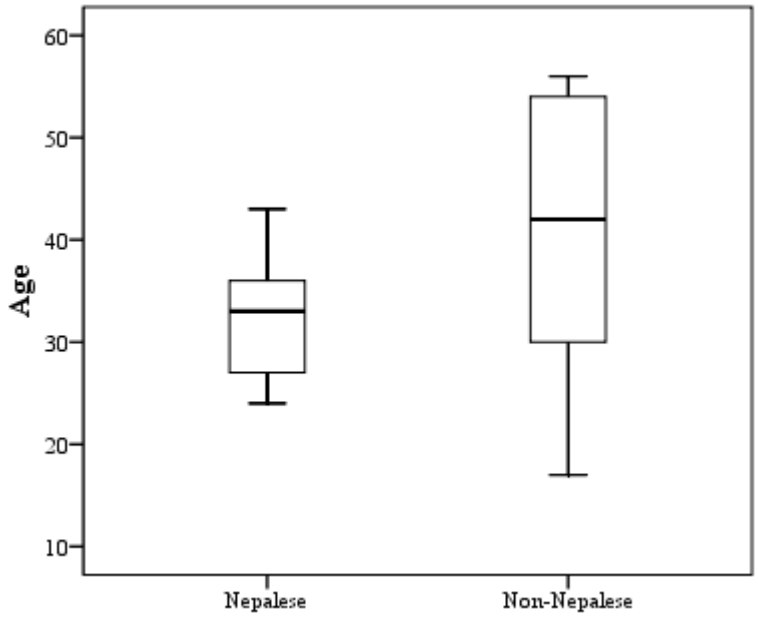

Figure 4-2 Age distribution by nationality
Nepalese climbers were significantly younger than non-Nepalese climbers (P= 0.043).

Number of nights required to reach EBC

The mean number of nights taken by the participants to reach the EBC was 6.10. The minimum was 2 and the maximum 17 nights. On analysis by nationality, there was a significant difference between Nepalese and non-Nepalese nationality in the number of nights required to reach EBC (Z= -4.073, P= 0.000), Nepalese participants needing on an average 4.5±2.45 nights and non-Nepalese participants needing 10.45±3.45 nights to reach EBC. Participants from treatment arm in comparison to placebo arm took longer time to get to Everest Base Camp from Lukla, but the difference was not significant.

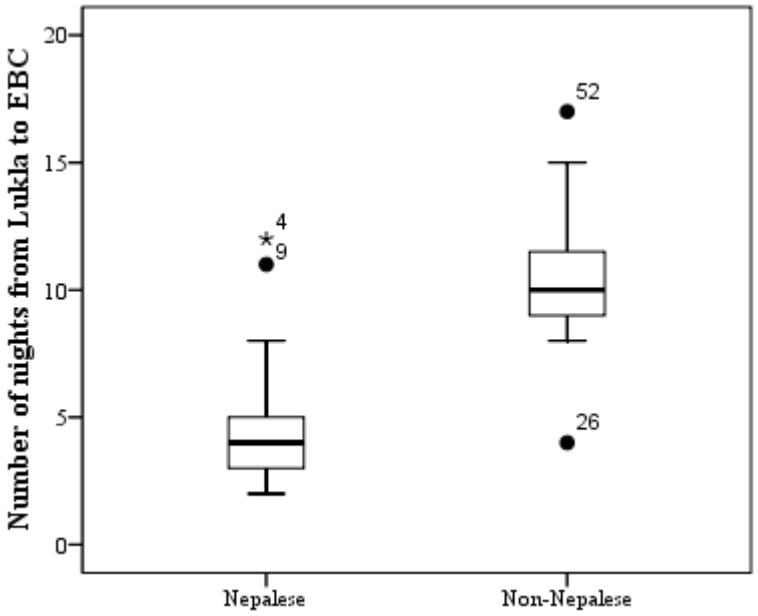

Figure 4-3 Number of nights taken by Nepalese and non-Nepalese climbers from Lukla to reach EBC
Nepalese climbers took much less number of nights (P= 0.000). This exposes them to higher risks of altitude illness.

Use of prescribed medication

Ten out of the 52 participants were taking some form of treatment at baseline. Of the medications in use were non-steroidal anti-inflammatory drugs (celecoxib and paracetamol alone or as combination), glatiramer (copaxone) for multiple sclerosis, alendronate, metaxalone, levothyroxine, omeprazole, vitamin tablets, guaiafenesin and dextromethorphan. Guaiafenesin was taken as a pro re nata prescription by 1 participant and dextromethorphan by 1 participant. These anti-tussives were not in the exclusion criteria. On analysis by nationality, 3 Nepalese participants used prescribed medication, those being paracetamol, omeprazole and throat lozenges. Other medications were used by non-Nepalese climbers. Only 1 non-Nepalese enrollee took acetazolamide while trekking up to the base camp of Everest.

Presence of Allergies

None of the participants reported having any previous allergies at the time of enrollment.

Long term illness

Three participants responded that they suffered from long term health conditions. One non-Nepalese participant had multiple sclerosis. Of the 2

Nepalese participants, one suffered from depression and the second from alcoholism.

Breathlessness

Fifty-one participants responded to this question. 31 (59.6%) responded to not having any kind of breathlessness at EBC at baseline, 14 (26.9%) had mild whereas 6 (11.5%) reported moderate breathlessness. There was no report of severe or incapacitating breathlessness at baseline among participants. There was a significant difference between Nepalese and non-Nepalese nationality in occurrence of breathlessness (χ^2=7.17, P= 0.028).

Table 4-2 Distribution of breathlessness by nationality

Significant difference was observed between the Nepalese and non-Nepalese participants of the study (P= 0.028).

		Nepalese	Non-Nepalese	χ^2	P
Breathlessness	None	25	6	7.17	0.028
	Mild	12	2		
	Moderate	2	4		

4.2. Improvement of cough

The primary outcome of the study was the variable improvement in cough. At follow-up visit, 34 of 40 (85%) participants mentioned that their cough had improved. Only 6 (15%) participants reported no change in cough status. Among those who reported improvement in cough, 4(10%) reported little improvement, 7 (17.5%) reported moderate improvement, 20 (50%) reported great improvement and 3 (7.5%) reported completely resolved cough. Median response was 4 (2.25-4).
In the placebo group, median response was 4 (greatly improved cough) (IQR 3-4), and in treatment group, median response was 4 (greatly improved cough) (IQR 1.75-4).
Among subjects taking treatment (18), 4 (22.2%) reported no improvement at all in HAC while the rest had some kind of improvement. 8 (44.44%) mentioned that their cough improved greatly, and 2 (11.11%) out of 18 subjects taking treatment mentioned having completely resolved cough. In subjects taking placebo (22), only 2 (9.1%) reported that they

had no improvement in cough, the rest reporting improvements of various degrees. 12 (54.5%) mentioned great improvement and 1 (4.55%) of 22 subjects mentioned having completely resolved cough. Fisher's exact test did not show any significant difference between placebo and treatment in improving the cough (P= 0.645).

Analysis of the data by significance of improvement in the treatment and placebo arms was carried out. In treatment arm, 8 of 18 (44.4%) did not report a significant improvement in cough, whilst a majority (56.4%) reporting that their cough improved significantly. In placebo group, 13 of 22 (59.1%) reported significant improvement in cough, and 40.9% reported otherwise. There is no statistically significant difference between placebo and treatment groups in terms of significant improvement of HAC (P= 0.538). The odds for significant improvement of HAC under treatment with combination of fluticasone 250 mcg and salmeterol 50 mcg in comparison to placebo is 0.865 with a 95% CI [0.246, 3.050].

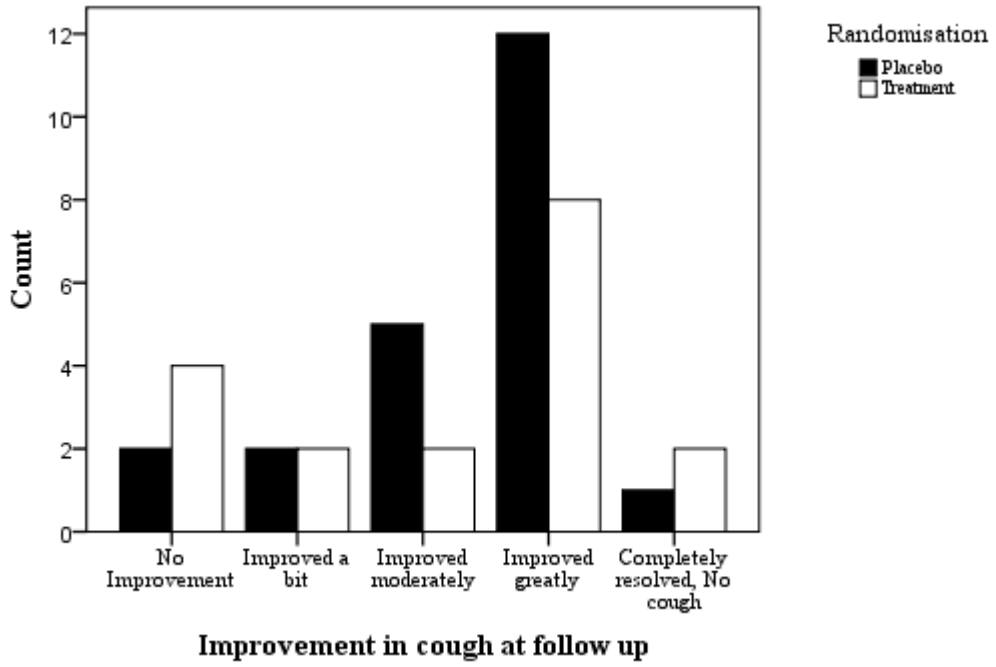

Figure 4-4 Distribution of improvement of cough by treatment arm

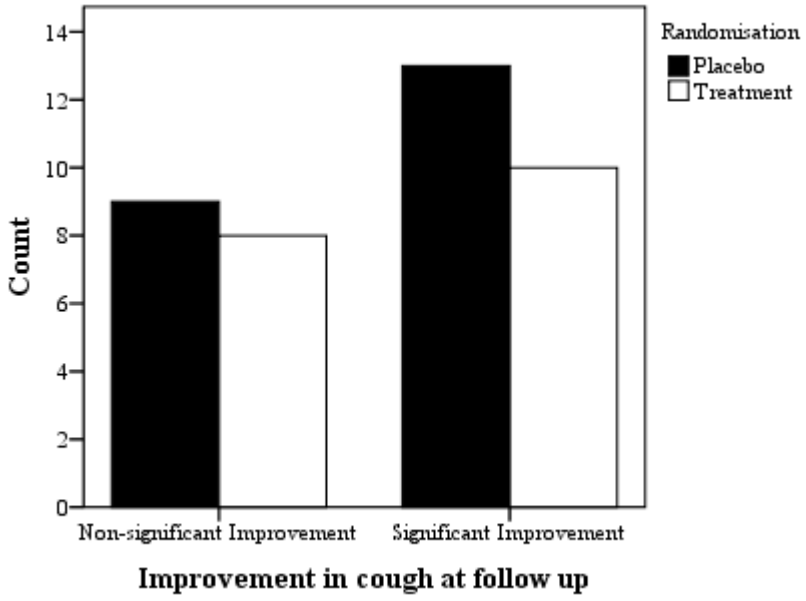

Figure 4-5 Distribution of significant improvement of cough at follow up

Table 4-3 Distribution of improvement in cough by randomization

		Randomization		
		Placebo	Treatment	
How Is Your Cough Now	No Improvement	2 (9.1)	4(22.2)	Fisher's Exact =2.84, P = 0.645
	Improved a bit	2(9.1)	2(11.1)	
	Improved moderately	5(22.7)	2(11.1)	
	Improved greatly	12(54.5)	8(44.4)	
	Completely resolved, No cough	1(4.5)	2(11.1)	
	Total	22(100)	18(100)	

Table 4-4 Distribution of significant improvement in cough by randomization

Variable	Groups	Randomization		P (Fisher's Exact)
		Placebo	Treatment	
Improvement of Cough	No Significant Improvement of Cough	**9**	**8**	0.538
	Significant Improvement of Cough	**13**	**10**	
Total		22	18	

Effect on nationality on the response to the primary outcome question was analyzed across arms. Comparing Nepalese participants versus non-Nepalese participants, there was no significant difference in the response to subjective patient reported improvement in cough at follow up (Z= -1.84, P= 0.066).

Correlation of improvement in cough to other variables

MLCQ score at follow up

In placebo arm, we found a significant correlation of improvement of cough with the MLCQ score at follow up (Spearman's rho= 0.70, P= 0.000). Significant correlation was also seen between improvement of cough and change in MLCQ score from baseline values (Spearman's rho= 0.47, P= 0.033).

In treatment arm also, correlation between improvement of cough and MLCQ score at follow up was significant (Spearman's rho= 0.85, P= 0.000). There was also a significant correlation between improvement of cough and change in MLCQ score from baseline values (Spearman's rho= 0.82, P= 0.000).

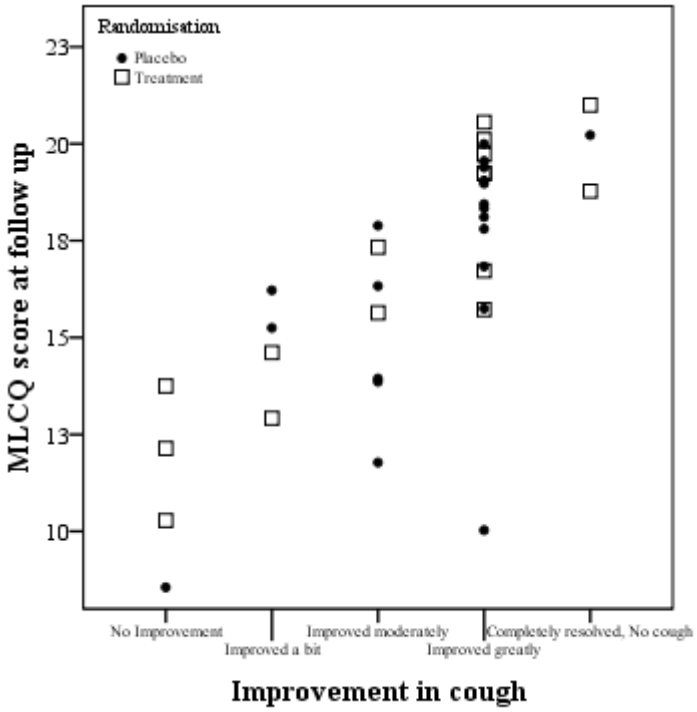

Figure 4-6 MLCQ score at follow up to improvement in cough scatterplot

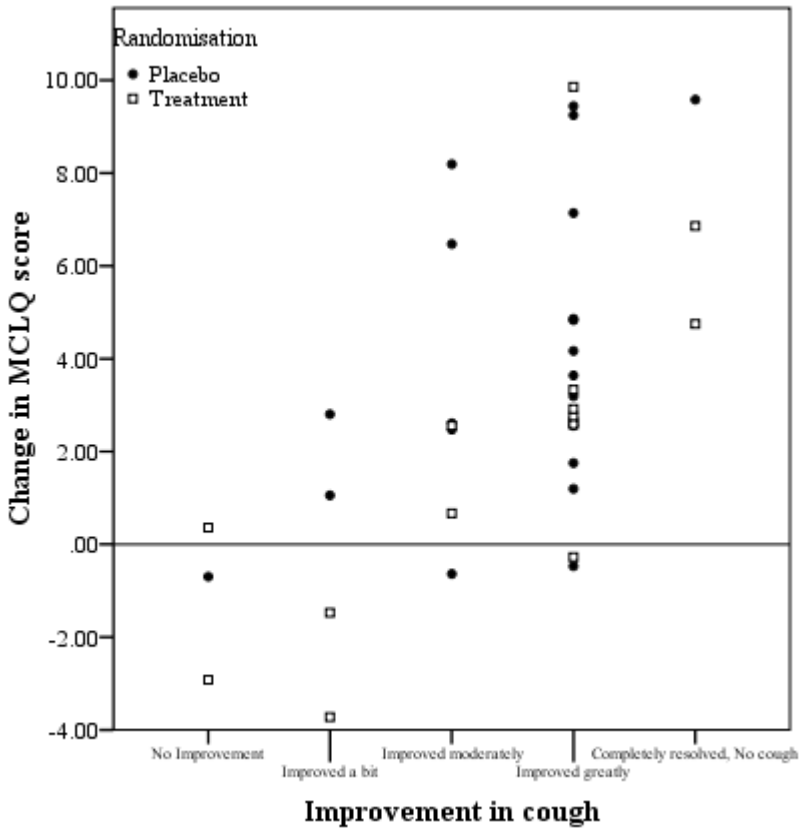

Figure 4-7 Change in MLCQ score to improvement in cough scatterplot

Clinical variables

Pulse rate, blood pressure, and oxygen saturation at follow up or change in their values from baseline did not correlate with improvement in HAC at follow up.

Respiratory function

Change in FEV1 values from baseline showed a significant positive correlation with improvement in cough in the treatment arm (Spearman's rho= 0.56, P= 0.015) and a significant negative correlation with improvement in cough in the placebo arm (Spearman's rho= -0.50, P= 0.023).

PEF values or change in PEF did not correlate with improvement in cough at follow up.

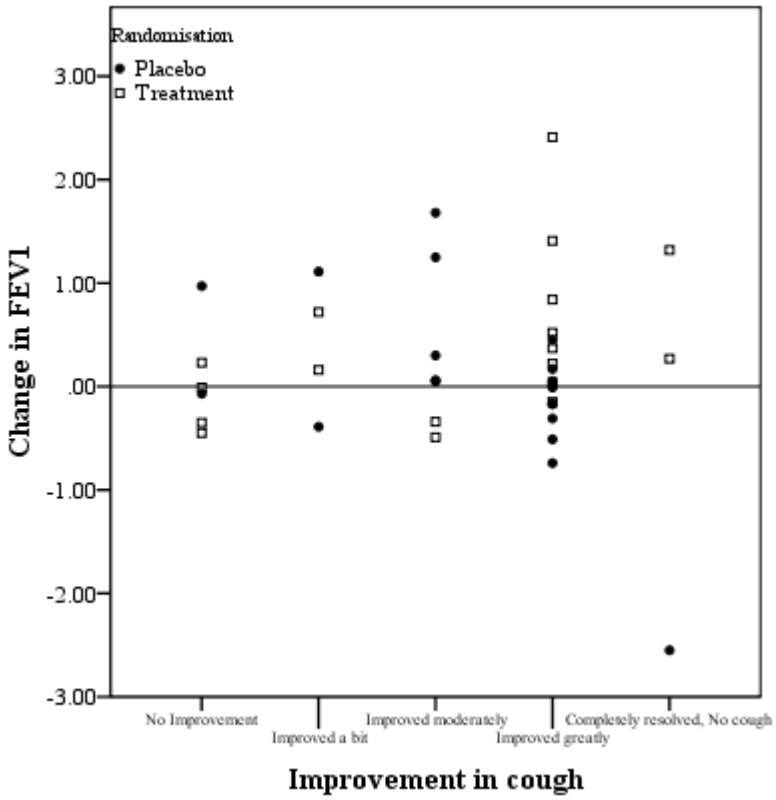

Figure 4-8 Association between change in FEV1 and improvement in cough

4.3. Quality of life at baseline

4.3.1. MLCQ score

MLCQ was administered to all participants at baseline and response was collected from all 52 enrollees except for 1 participant failing to respond to questionnaire item number 10. Mean MLCQ score at baseline was 13.54±3.08. Also at baseline, mean physical domain score for MLCQ was 4.42±0.99, mean psychological domain score was 4.56±1.247 and mean social domain score was 4.58±1.48.

MLCQ score by nationality of participants

Mean MLCQ score was 13.55±3.13 for Nepalese participants, whereas for non-Nepalese participants mean score was 13.49±3.05. There was no difference in quality of life at baseline among Nepalese climbers as compared to the non-Nepalese climbers at enrollment (Z= -0.16, P= 0.876). Similarly, the mean physical domain score for Nepalese participants was 4.36±0.98 and for non-Nepalese participants 4.61±1.06; there being no statistical difference based on nationality (Z= -0.77, P=

0.443). Mean psychological domain score was 4.50±1.31 for Nepalese and 4.69±1.08 for non-Nepalese participants; also without a statistical difference (Z= -0.66, P= 0.512). Mean social domain scores at baseline for Nepalese population was 4.69±1.57. For non-Nepalese participants, mean social domain score was 4.19±1.19 which was also not different statistically (Z= -1.20, P= 0.231).

MLCQ scores by gender

Analyzing the MLCQ scores by gender, we found that in males, the mean score was slightly higher (13.55±3.06) than in females (13.41±3.55). However, there was no statistical difference between genders (Z= -0.06, P= 0.953). Mean physical score in males (4.42±0.98) was very similar to that in females (4.43±1.16) with Z-value -0.15 and P 0.884. Mean psychological score was also similar between male participants (4.54±1.28) and female participants (4.53±1.14) in the study population. Test statistics for difference in psychological domain score were Z -0.04 and P 0.966. Mean social domain score showed a slight difference however not statistically (Z= -0.29, P= 0.774). The male gender scored higher (4.59±1.50) in an average as compared to female counterparts in the study (4.46±1.57).

MLCQ scores by treatment arm

MLCQ scores at baseline were also studied to find any differences between treatment arm and placebo arm. At baseline, mean MLCQ score in the placebo arm was 12.66±3.33 and in the treatment arm was 14.60±2.41. This difference was significant statistically (Z= -2.10, P= 0.028). On exploring domain scores, difference was found between the arms in physical (Z= -2.38, P= 0.017) domain. Mean physical domain score for placebo was 4.12±1.04 and for treatment arm was 4.79±0.81. Similarly, mean psychological domain score for placebo arm was 4.36±1.32, whereas for treatment arm, it was 4.77±1.16. Social domain score was 4.19±1.65 for placebo arm and it was 5.04±1.14 for treatment arm. Tests failed to show significant statistical difference between placebo and treatment arms in psychological (Z= -1.27, P= 0.205) and social domains (Z= -1.90, P= 0.058).

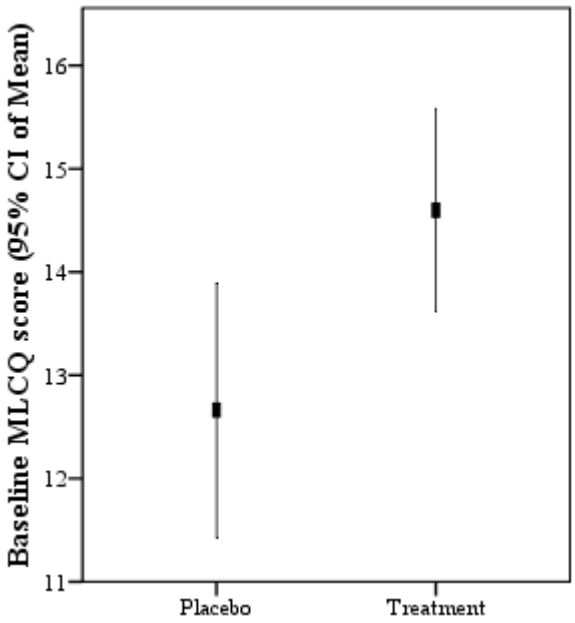

Figure 4-9 Baseline mean MLCQ score with 95% CI

There was a significant difference (P= 0.028) between the two arms at baseline.

Table 4-5 MLCQ score and domain scores at baseline

	Placebo	Treatment	P	Total
MLCQ Score	12.82±3.29	14.51±2.43	0.028	13.54±3.08
Physical Domain	4.16±1.03	4.80±0.83	0.017	4.42±0.99
Psychological Domain	4.4±1.33	4.72±1.16	0.205	4.56±1.25
Social Domain	4.25±1.65	4.99±1.14	0.058	4.58±1.48

On analyzing the Modified LCQ, the reliability of the 19-item questionnaire, calculated in terms of Cronbach's alpha, was 0.816.

On analyzing individual questionnaire items, 4 items showed significant difference at enrollment between placebo and treatment arms by Mann Whitney U test.

a. Cough interferes with the overall enjoyment of trek (Z= -3.850, P= 0.000)
b. During trek, has cough disturbed your sleep?(Z= -2.806, P= 0.005)
c. During the trek, my cough has made me feel frustrated.(Z= -2.460, P= 0.014)
d. During the trek, have you had a lot of energy? (Z= -2.223, P= 0.026)

Subjects receiving treatment had a higher score, denoting better quality of life, than the placebo in these 4 items. There was no difference between

placebo and treatment groups in other questionnaire items during enrollment.

4.3.2. Physical domain:

Questionnaire items falling in the physical domain were questions 1, 2, 3, 4, 10, 11, 12, 14 and 15. These questions assessed the self-reported quality of life in terms of physical presence of cough, pain associated, sputum production, tiredness attributable, exacerbation by fumes, loss of sleep, frequency of coughing bouts, hoarse voice and energy levels in the presence of cough. Most subjects came for treatment when median subjective cough perception was 3.5. Subjects had chest or stomach pains infrequently (median score 7), were not bothered by sputum production (median score 5), coughing bouts were present several times during the day (median score 3), occasionally suffered from hoarse voice (median score 5). Median scores and inter-quartile range for each questionnaire item were compared across treatment arms and represented in the table.

Table 4-6 Physical domain questionnaire items at baseline

Physical Domain	Placebo			Treatment		
	N	Median	IQR	N	Median	IQR
Have you been troubled by a cough during your trek?	28	3.50	2.00-5.00	24	3.50	2.25-4.00
During your trek, had chest or stomach pains due to cough?	28	6.00	4.00-7.00	24	7.00	5.00-7.00
During your trek, have you been tired because of your cough?	28	5.00	3.00-7.00	24	5.00	4.00-7.00
Have you been bothered by sputum production when you cough?	28	5.00	4.00-6.00	24	5.50	4.00-7.00
During trek, exposure to smoke or fumes makes me cough	28	4.50	2.00-6.00	23	5.00	5.00-7.00
During trek, has cough disturbed your sleep?	28	4.00	2.00-5.00	24	6.00	4.00-7.00
If troubled by cough, how many times/day have had coughing bouts?	28	3.00	1.25-3.00	24	3.00	2.00-4.00
During trek, have you suffered from hoarse voice from cough?	28	5.00	2.50-6.00	24	5.00	3.00-7.00
During trek, have you had a lot of energy?	28	4.00	2.00-6.00	24	6.00	4.00-7.00

4.3.3. Psychological domain:

Questionnaire items falling in the psychological domain were questions 5, 6, 7, 13, 16 and 17. These questions assessed the self-reported control, embarrassment, anxiety, frustration, worry and concern because of the presence of cough. The participants were not embarrassed by the cough (median score 5), and generally not concerned that other people thought

there was something wrong with them due to cough. Median scores and IQR were compared across treatment arms and are represented in the table.

Table 4-7 Psychological domain questionnaire items at baseline

Psychological Domain	Placebo			Treatment		
	N	Median	IQR	N	Median	IQR
During your trek, have you felt in control of your cough?	28	4.50	2.25-6.00	24	3.50	2.00-5.75
How often during your trek have you felt embarrassed by coughing?	28	5.00	4.00-7.00	24	5.50	4.00-7.00
During the trek, my cough has made me feel anxious	28	4.00	2.00-6.00	24	5.00	3.00-6.00
During trek, my cough has made me feel frustrated	28	3.00	2.00-5.00	24	5.00	4.00-7.00
During trek, have you worried cough may indicate serious illness	28	5.00	2.50-7.00	24	7.00	3.25-7.00
Concerned other people think something wrong w/you due to cough?	28	6.00	2.00-7.00	24	5.50	3.00-7.00

4.3.4. Social domain:

Questionnaire items in this domain were 8, 9, 18 and 19. Social domain assessed the self-reported interference of cough in daily jobs, interference in overall enjoyment, interruption in communications and annoyance of others as a direct result of cough. Subjects felt that the cough did not interfere with the ability to exercise or other tasks (median score 5). Median and IQR distribution across treatment arms is represented in the table.

Table 4-8 Social domain questionnaire items at baseline

Social Domain	Placebo			Treatment		
	N	Median	IQR	N	Median	IQR
During trek cough interfered w/ability to exercise or other task	28	5.00	4.00-7.00	24	5.00	4.00-7.00
Cough interferes with overall enjoyment of trek	28	3.00	1.25-4.75	24	5.50	4.00-7.00
During trek, my cough has interrupted conversation	28	4.00	3.00-6.75	24	4.50	3.25-7.00
During trek, my cough has annoyed fellow trekkers/tent partner	28	4.00	3.00-7.00	24	5.00	4.00-7.00

4.4. Quality of life at follow up

4.4.1. MLCQ score

At follow up, self-administered MLCQ was analyzed to assess the change in the quality of life brought about by the different treatment arms. Complete response from 42 participants was available for analysis. The items in MLCQ could get a score from 1-7, where 1 is the worst quality of life and 7 is the best quality of life possible. At follow-up, Cronbach's alpha for MLCQ was 0.906.

At follow up, mean MLCQ score was 16.34±3.28, a significant improvement (P= 0.000) from the baseline value. In placebo arm, the

score was 16.09±3.39 at follow up, also a significant improvement from baseline values (P= 0.000). The mean change in MLCQ score from baseline value in placebo arm was 3.92 with 95% CI 2.56-5.28. In treatment arm, the follow up value of 16.87±3.21 was significantly different from baseline value (P= 0.032). The mean change in the treatment group was 2.21 with 95% CI 0.36-4.06. There was no statistical difference between the treatment arms in the follow up values (P= 0.594) as well as between the mean change in MLCQ scores in the respective arms (P= 0.166).

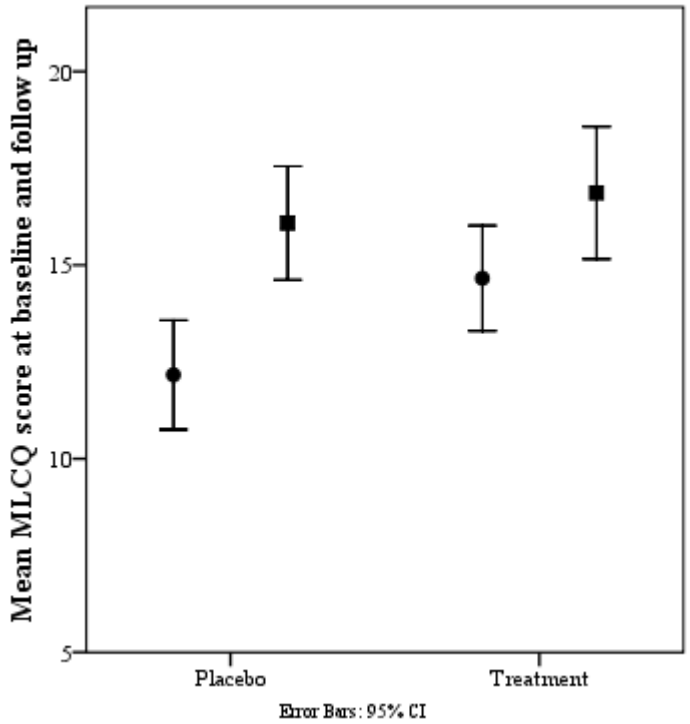

Figure 4-10 Mean MLCQ score and 95% CI of mean at baseline and follow up

Table 4-9 MLCQ score and domain scores by randomization at follow up

	Placebo	Treatment	P	Total
MLCQ Score	16.09±3.39	16.87±3.21	0.594	16.34±3.28
Physical Domain	5.19±.86	5.53±1.13	0.403	5.29±1.02
Psychological Domain	5.41±1.38	5.66±1.04	0.873	5.45±1.25
Social Domain	5.41±1.38	5.66±1.04	0.692	5.49±1.47

Table 4-10 MLCQ score and domain scores comparison inside study arms

	Placebo			Treatment			Total		
	Baseline	Follow Up	P	Baseline	Follow Up	P	Baseline	Follow Up	P

MLCQ Score	12.82±3.29	16.09±3.39	0.000	14.51±2.43	16.87±3.21	0.032	13.54±3.08	16.34±3.28	0.000
Physical Domain	4.16±1.03	5.19±.86	0.000	4.80±0.83	5.53±1.13	0.046	4.42±0.99	5.29±1.02	0.000
Psychological Domain	4.4±1.33	5.41±1.38	0.003	4.72±1.16	5.66±1.04	0.06	4.56±1.25	5.45±1.25	0.000
Social Domain	4.25±1.65	5.41±1.38	0.000	4.99±1.14	5.66±1.04	0.13	4.58±1.48	5.49±1.47	0.000

4.4.2. Physical domain:

In placebo arm, mean physical domain score increased significantly to 5.19±0.86 (P= 0.000) from baseline value. In treatment arm, the follow up value of 5.53±1.13 was also significantly different from baseline values (P= 0.046). However there was no significant difference between placebo and treatment arms at follow up.

Comparing median scores for individual questionnaire items in the physical domain between treatment and placebo arms at baseline and follow up, a general trend of increase in scores in seen in most questionnaire items. Participants were less troubled by cough at EBC or above at follow up in both placebo and treatment arms. Tiredness because of cough at baseline in both arms improved to a median score of 6 at follow up. Being bothered by sputum production in placebo arm remained unchanged but the median score improved in treatment arm. Exposure to fumes and smoke causing cough remained unchanged in treatment arm, and improved in the placebo arm. Disturbance in sleep attributable to cough also improved in both arms and a slight improvement in median scores was noted in the frequency of coughing bouts per day. Hoarse voice from cough improved to a median score of 7 from a median score of 5 in both arms.

Table 4-11 Physical domain summary of statistics at follow up

Physical Domain	Placebo			Treatment		
	N	Median	IQR	N	Median	IQR
Have you been troubled by a cough during your trek?	24	5.00	4.00-5.75	18	5.00	3.00-6.25
During your trek, had chest or stomach pains due to cough?	24	7.00	5.25-7.00	19	6.00	4.00-7.00
During your trek, have you been tired because of your cough?	23	6.00	5.00-7.00	19	6.00	4.00-7.00
Have you been bothered by sputum production when you cough?	24	5.00	4.00-5.75	19	6.00	3.00-7.00
During trek, exposure to smoke or fumes makes me cough	24	5.00	4.00-6.75	18	5.00	4.00-7.00
During trek, has cough disturbed your sleep?	24	6.00	4.25-7.00	19	7.00	5.00-7.00
If troubled by cough, how many times/day have had coughing bouts?	24	4.00	3.00-5.00	19	4.00	3.00-6.00
During trek, have you suffered from hoarse voice from cough?	24	7.00	5.00-7.00	19	7.00	6.00-7.00
During trek, have you had a lot of energy?	24	6.00	3.25-6.00	19	6.00	4.00-7.00

4.4.3. Psychological domain:

Psychological domain scores improved significantly in placebo group at follow up to 5.41±1.38 (P= 0.003). In treatment arm, there was improvement in mean scores to 5.66±1.04 but the difference from baseline values was not significant (P= 0.058). At follow up, however, placebo and treatment arms did not show a statistically significant difference (P= 0.873).

Looking at the individual questionnaire items, there was a trend for positive change in median scores at follow up. Feeling of being in control of cough improved in both arms at follow up. Embarrassment due to cough in both arms at follow up improved to a median score of 7. There was overall improvement in feeling of anxiety in placebo arm, and strong improvement in frustration levels.

Table 4-12 Psychological domain summary of statistic at follow up

Psychological Domain	Placebo			Treatment		
	N	Median	IQR	N	Median	IQR
During your trek, have you felt in control of your cough?	24	5.00	3.00-6.75	19	5.00	3.00-7.00
How often during your trek have you felt embarrassed by coughing?	24	7.00	4.00-7.00	19	7.00	4.00-7.00
During the trek, my cough has made me feel anxious	24	6.50	4.00-7.00	19	5.00	4.00-7.00
During trek, my cough has made me feel frustrated	24	6.50	4.00-7.00	19	7.00	4.00-7.00
During trek, have you worried cough may indicate serious illness	24	6.00	4.00-7.00	19	6.00	5.00-7.00
Concerned other people think something wrong w/you due to cough?	24	6.00	4.00-7.00	19	7.00	5.00-7.00

4.4.4. Social domain:

Mean domain scores in social domain showed an increase at follow up from the baseline values. In placebo arm, the mean follow up value of 5.41±1.38 was significantly different from the baseline value (P= 0.000). However, in treatment arm, the follow up value of 5.66±1.04 was not significantly different from the baseline values (P= 0.127). There was no significant difference between the arms in the follow up values for the social domain (P= 0.692).

There was improvement in median score in both arms in the interference by cough to exercise. There was improvement in the median score for cough interfering in the overall enjoyment of the trek in placebo arm. There was big improvement in the median score at follow up in both arms in interruption of conversation by cough and annoyance of fellow trekkers or tent partners due to cough.

Table 4-13 Social domain summary of statistics at follow up

Social Domain	Placebo			Treatment		
	N	Median	IQR	N	Median	IQR
During trek cough interfered w/ability to exercise or other task	24	6.00	4.00-7.00	19	6.00	5.00-7.00
Cough interferes with overall enjoyment of trek	24	6.00	4.00-7.00	19	5.00	4.00-7.00
During trek, my cough has interrupted conversation	24	5.50	4.00-7.00	19	7.00	3.00-7.00
During trek, my cough has annoyed fellow trekkers/tent partner	24	6.00	4.00-7.00	19	7.00	6.00-7.00

4.5. Relation of cough to exercise

4.5.1. At baseline

This question was put together with the cough questionnaire, and was a self-reported 3 scale question with responses to the question "If you have a cough, how often is it related to exercise?" The responses possible were 'Only brought on by exercise', 'Made worse by exercise', and 'Not related to exercise'.

At baseline, 8 out of 52 (15.4%) respondents answered that their cough was brought on by exercise. In contrast, 21 (40.4%) responded that their cough was made worse by exercise and 23 (44.2%) responded that exercise was not related to cough in any way. In the placebo arm, the responses were 2 (7.1%), 9 (32.1%), and 17 (60.7%) respectively. In the treatment arm, the responses were 6 (25%), 12 (50%) and 6 (25%) respectively. On analyzing the difference between arms with χ^2 test, there was a significant statistical difference between treatment arms at baseline (χ^2=7.43, df= 2, P= 0.024).

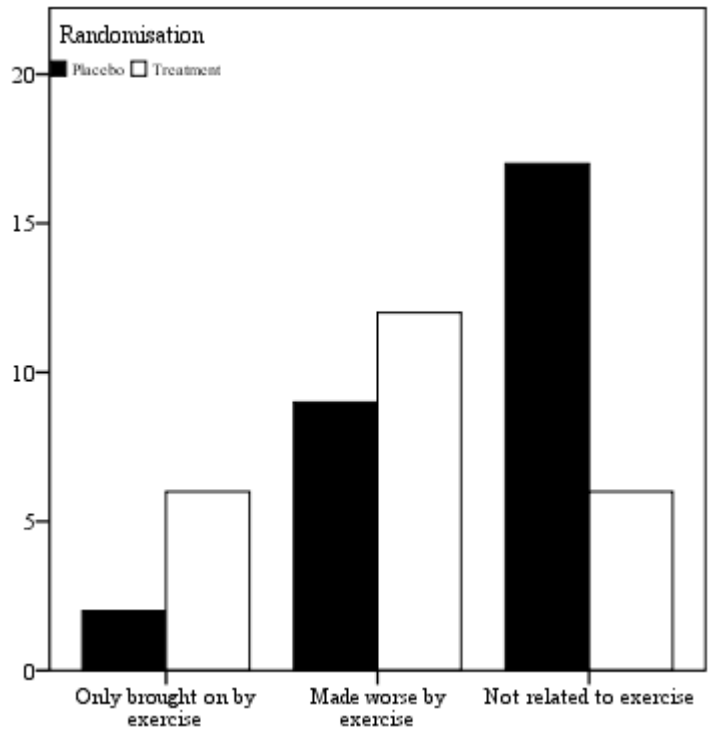

Figure 4-11 Relation of HAC with exercise at baseline

Table 4-14 Relation of cough to exercise at baseline

		Randomization		χ^2	df	P
		Placebo	Treatment			
If you have a cough, how often is it related to exercise?	Only brought on by exercise	2	6	7.426	2	0.024
	Made worse by exercise	9	12			
	Not related to exercise	17	6			

4.5.2. At follow up

At follow up, none of the participants in the treatment arm responded that the cough was brought on only by exercise, whereas 3 participants (12.5%) responded that exercise was the cause for cough.7 participants in placebo (29.2%) and 7 in treatment arm (41.2%) responded that the cough was made worse by exercise. 14 (58.3%) in the placebo arm and 10 (58.8%) in the treatment arm responded at follow up that their cough was not related to exercise.

On χ^2 test between placebo and treatment arms, there was no difference between the arms at follow up in the distribution of participants regarding the relation of cough to exercise.

Table 4-15 Distribution of relation of cough to exercise by treatment arm

		Randomization		χ^2	df	P
		Placebo	Treatment			
If you have a cough, how often is it related to exercise?	Only brought on by exercise	3	0	2.546	2	0.280
	Made worse by exercise	7	7			
	Not related to exercise	14	10			

4.6. Altitude of HAC occurrence

Most of the participants reported that their cough developed when they reached an altitude of 5000-5999 meters. Second most frequent altitude where the HAC started was 4000-4999 meters. This proportion was similar for Nepalese and non-Nepalese participants of the study.

Table 4-16 Altitude of HAC occurrence

Altitude	Total		Placebo		Treatment		Nepalese		Non-Nepalese	
	N	Percent	N	Percent	N	Percent	N	Percent	N	Percent
3000-3999 m	2	3.8	2	7.1			1	2.6	1	7.7
4000-4999 m	10	19.2	6	21.4	4	16.7	7	17.9	3	23.1
5000-5999 m	32	61.5	15	53.6	17	70.8	24	61.5	8	61.5
Above 6000 m	8	15.4	5	17.9	3	12.5	7	17.9	1	7.7
Total	52	100	28	100	24	100	39	100	13	100

4.7. Clinical Variables at baseline and follow up

Pulse rate

At baseline, average pulse rate for participants with HAC was 82.37±15.48 per minute. On analyzing by nationality, Nepalese participants were found to have lower (81.51±15.50 per minute) pulse rate than their non-Nepalese counterparts (84.92±15.77 per minute). This difference was not significant between the groups compared (Z= -0.29, P= 0.775). Female climbers were found to have slightly higher pulse rates (85.17±14.26 per minute) than their male counterparts (82.00±15.74 per minute), but the difference was not significant (Z= -0.30, P= 0.763). Analyzing by treatment arms, baseline pulse rate in treatment arm was 81.29±16.90 per minute, while in placebo arm, 83.29±14.40 per minute. There was no difference on comparison of the two arms (Z= -0.36, P= 0.693).

On follow up, mean pulse rate for the placebo arm was 80.77±9.99 per minute, with a mean change of -3.18 per minute (95% CI -9.26, 2.90) from its baseline values. This decrease was not significantly different though (P= 0.235). In the treatment arm, the pulse rate at follow up was 87.38±18.12 per minute, a mean change of 5.29 per minute (95% CI -3.40, 13.99) from the baseline values. The difference with baseline values was not significant (P= 0.199). Although the mean change in pulse rate between arms was not significantly different (Z= -1.79, P= 0.074), this change in treatment arm is in opposite direction to that of placebo arm. There was no difference between placebo and treatment arms at follow up (P= 0.304).

Table 4-17 Pulse rate

	Pulse Rate (per minute)			
	Baseline	Follow Up	P[a]	Change
Placebo	83.04±14.61	80.77±9.99	0.235	-3.18±13.71
Treatment	81.68±17.56	87.38±18.12	0.199	5.29±16.92
P[b]	0.693	0.304	-	0.074
Total	82.37±15.48	82.65±14.22	0.995	-0.19±14.98
a: P-value for before after comparison (row) b: P-value for between the groups comparison (column)				

Oxygen Saturation

Oxygen saturation measured at baseline was in average 83.06±3.84 percentage. This was lower in Nepalese participants (82.36±3.89 percent) than non-Nepalese participants (85.15±2.88). The difference between the groups was significant in this case (Z= -2.16, P= 0.031). Male participants seemed to have slightly lower oxygen saturation (82.89±3.88 percent) than their female counterparts (84.33±3.50 percent), there being no difference between the groups (Z= -1.04, P= 0.300). Analyzing the variable at baseline by treatment arm, participants in treatment arm had slightly lower (82.58±4.72 percent) saturation than their counterparts in the placebo arm (83.46±2.91 percent). However there was no difference in oxygen saturation between the treatment and placebo arms (Z= -0.76, P= 0.449).

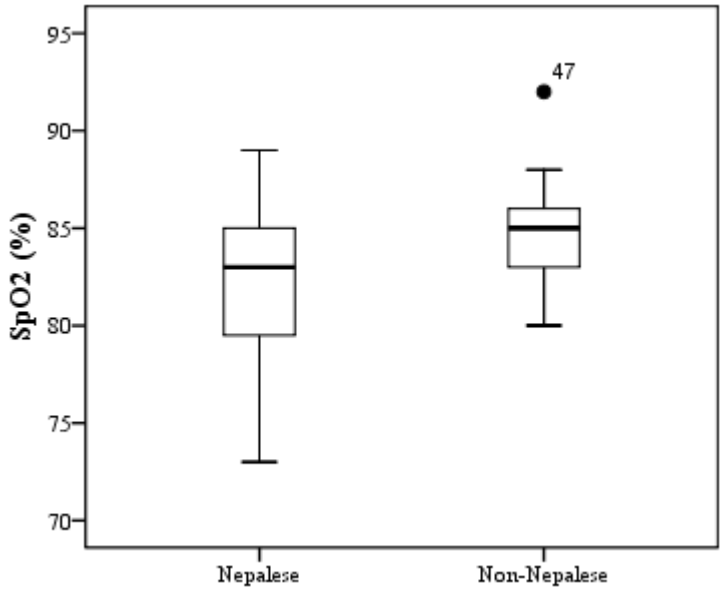

Figure 4-12 Distribution of oxygen saturation in Nepalese and non-Nepalese participants at baseline

At follow up, oxygen saturation showed tendency in both arms to increase. With the arms combined, the total increase was significant from baseline 83.06±3.84 to follow up value 84.42±4.99 (P= 0.025). On analysis of the arms separately, mean increase in placebo arm was from 1.32 percent (95% CI -0.17, 2.81) to a mean follow up value of 84.82±4.03 percent. This increase was not significant (P= 0.088). In treatment arm, the percentage saturation increased on an average by 1.65 percent (95% CI -1.32, 4.61) to 83.38±6.56 percent, a change not significant (P= 0.169). There was no difference in the mean increase of oxygen saturation between the arms (Z= -0.03, P= 0.980). There was no difference between placebo arm and treatment arm in the follow up oxygen saturation values (P= 0.806).

Table 4-18 Oxygen saturation

	SpO2 (%)			
	Baseline	Follow Up	P[a]	Change
Placebo	83.63±2.83	84.82±4.03	0.088	1.32±3.36
Treatment	82.32±4.84	83.38±6.56	0.169	1.65±5.77
P[b]	0.449	0.806	-	0.980
Total	83.06±3.84	84.42±4.99	0.025	1.37±4.36
a: P-value for before after comparison (row) b: P-value for between the groups comparison (column)				

Blood Pressure

At baseline, average systolic blood pressure (SBP) was 133.43±14.99 mmHg. Diastolic blood pressure (DBP) on average was 86.20±12.51 mmHg. Among the Nepalese participants, SBP was 135.54±15.41 mmHg and DBP was87.90±13.31 mmHg. Among non-Nepalese participants, SBP was 126.58±11.61 mmHg and DBP was 80.67±7.43 mmHg. This comparison by nationality for SBP (Z= -1.87, P= 0.061) and for DBP (Z= -1.90, P= 0.058) were statistically not significant although there was difference between Nepalese and non-Nepalese participants was seen. In the treatment arm, SBP was 137.78±17.13 mmHg and DBP was 89.04±13.08 mmHg. In the placebo arm, SBP was 129.86±12.16 mmHg and DBP was 83.86±11.73 mmHg. Between treatment arms, the difference seen in SBP (Z= -1.69, P= 0.091) and DBP (Z= -1.30, P= 0.192) was not significant.

Systolic and diastolic blood pressures did not show significant fluctuations in both arms between baseline data and follow-up data. SBP in the placebo and treatment arms decreased on follow up to 128.32±16.45 mmHg and 134.13±17.24 mmHg respectively. The mean change in SBP in the placebo arm was -2.64 mmHg (95% CI -10.68, 5.40) and in treatment arm was -2.94 mmHg (95% CI -11.50, 5.63). There was no difference between the arms at follow up (P= 0.227). There was no difference in the mean changes between the arms too (P= 0.885). DBP showed a marginal increase to 84.27±14.41 mmHg from baseline value in the placebo arm. But the mean change was -2.91 mmHg (95% CI -9.59, 3.77). In the treatment arm, DBP took a dip to 86.19±14.28 mmHg. The mean change was -2.06 mmHg (95% CI -8.80, 4.69). There was no difference between the DBP values between arms at follow up. The mean changes in DBP did not reveal any significant differences between arms.

Table 4-19 Systolic and Diastolic blood pressure

	SBP (mmHg)				DBP (mmHg)			
	Baseline	Follow Up	P[a]	Change	Baseline	Follow Up	P[a]	Change
Placebo	129.48±12.23	128.32±16.45	0.279	-2.64±18.14	83.07±11.19	84.27±14.41	0.296	-2.91±15.07
Treatment	138.68±16.96	134.13±17.24	0.338	-2.94±16.65	89.45±13.23	86.19±14.28	0.678	-2.06±13.12
P[b]	0.091	0.227	-	0.885	0.192	0.721	-	0.784
Total	133.43±14.99	130.62±16.07	0.181	-2.95±16.92	86.20±12.51	84.71±13.90	0.251	-2.35±13.94
a: P-value for before after comparison (row) b: P-value for between the groups comparison (column)								

Peak expiratory flow

Measurement at baseline revealed an average PEF of 8.79±2.77 liters/second among all participants. Nepalese participants sported an average PEF of 8.24±2.65 liters/second. Average for non-Nepalese participants was 10.19±2.71 liters/second. There was a significant statistical difference in PEF by nationality in the study population (Z= -2.08, P= 0.037). PEF measurement by gender yielded no statistical difference between male and female participants. Average PEF for males in the study was 8.71±2.73 liters/second, whereas for females was 8.92±3.34 liters/second, with the Z-value being -0.14 and P-value 0.886. Average PEF value for placebo arm was higher (9.29±2.85 liters/second) than average PEF in the treatment arm (8.11±2.60 liters/second). However, there was no statistical difference between the treatment arms at baseline (Z= -1.55, P= 0.121).

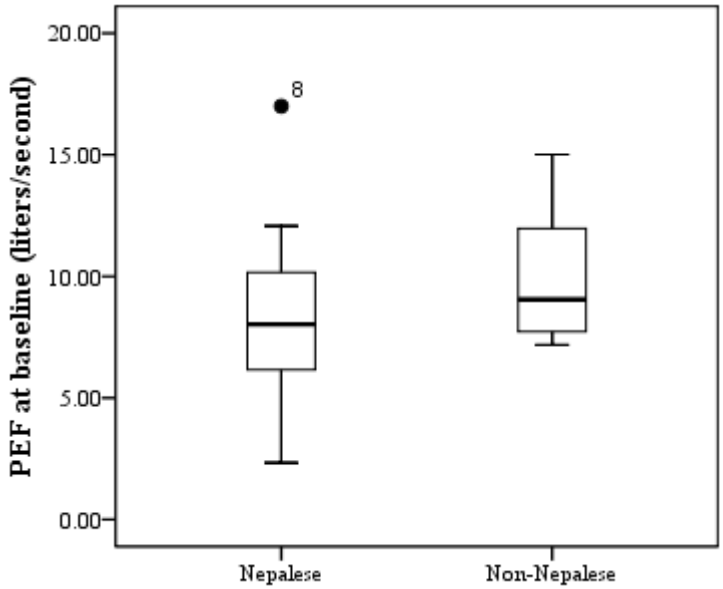

Figure 4-13 PEF distribution at baseline among Nepalese and non-Nepalese participants at baseline

PEF in placebo arm was 10.10±3.35 at follow up, significantly different from baseline values (P= 0.021). The mean difference in PEF from baseline values was 0.58 liters/second (95% CI -0.44, 1.61). In the treatment arm, PEF was 9.16±2.68 at follow up, which was not significantly different to baseline values. The mean difference in treatment arm was 0.70 liters/second with 95% CI -0.48, 1.87. The mean differences between the arms did not show any significant differences (Z= -0.49, P= 0.625).

Table 4-20 Peak expiratory flow

	PEF (liters per second)			
	Baseline	Follow Up	P[a]	Change
Placebo	9.29±2.85	10.10±3.35	0.021	0.59±2.32
Treatment	7.89±2.57	9.16±2.68	0.117	0.70±2.29
P[b]	0.121	0.076	-	0.625
Total	8.79±2.77	9.54±2.99	0.006	0.53±2.19
a: P-value for before after comparison (row) b: P-value for between the groups comparison (column)				

Forced expiratory volume in first second (FEV1)

Mean FEV1 at baseline in the study population was 3.62±1.01 liters. Mean among Nepalese participants was 3.61±0.98 liters and among non-Nepalese participants 3.65±1.15 liters. There was no significant statistical difference in FEV1 on comparing by nationality (Z= -0.20, P= 0.846). Comparing by gender, male participants had a higher average FEV1 (3.70±0.95 liters) than female climbers (3.03±1.35 liters). This was statistically different (Z= -2.09, P= 0.037).

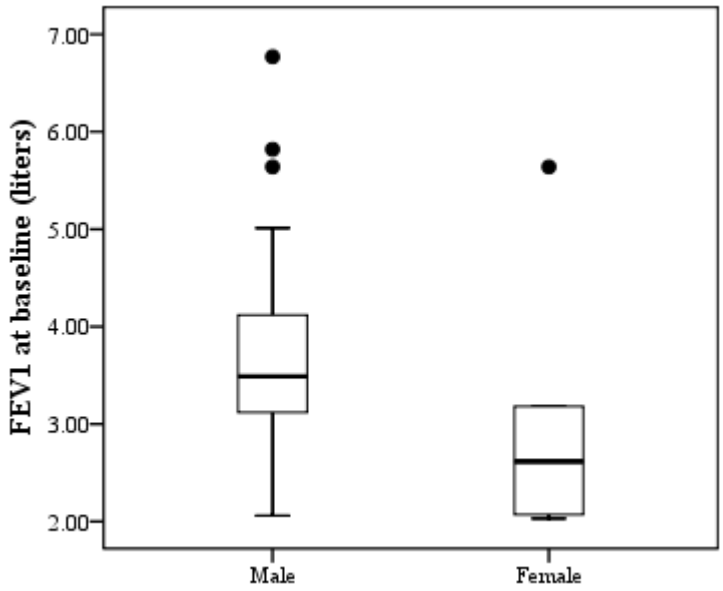

Figure 4-14 FEV1 distribution by gender at baseline

Similarly, analyzing at baseline by treatment arms, mean FEV1 was 3.85±1.08 liters in placebo and 3.36±0.88 liters in salmeterol/fluticasone treatment arm. There was no significant statistical difference between the treatment arms (Z= -1.56, P= 0.119) at baseline in this regard too. Standard and predicted values for Nepalese population are not available. FEV1 and PEF at enrollment are lower than predicted values for a 35 years 170 cm Caucasian male (predicted FEV1 3.96 liters, P= 0.02;

predicted PEF 9.57 liters/second, P= 0.046) [74, 75]. Using predicted values for Indian population for same age group [76], FEV1 is significantly higher (P= 0.033, predicted FEV1 = 3.31 liters).

On analyzing FEV1 values, the data showed an improvement over time in both treatment and placebo arms in this study. On analyzing total values at baseline and follow up, there was a significant change over time (P= 0.049). In placebo arm, there was a mean increase in FEV1 by 0.12 liters (95% CI -0.26, 0.49). Mean increase in the treatment arm was 0.39 liters (95% CI -0.04, 0.75). There was no difference between placebo and treatment arms in the increase in FEV1 from baseline (Z= -0.87, P= 0.383).

Table 4-21 FEV1

	FEV1 (liters)			
	Baseline	Follow Up	P[a]	Change
Placebo	3.85±1.08	3.95±1.04	0.369	0.11±0.85
Treatment	3.35±.87	3.88±.98	0.059	0.36±0.77
P[b]	0.119	0.633	-	0.383
Total	3.62±1.01	3.85±1.00	0.049	0.23±0.79
a: P-value for before after comparison (row) b: P-value for between the groups comparison (column)				

4.8. Symptom checklist at baseline

The 14-symptom checklist was analyzed to see the presence of accompanying symptoms in HAC. The symptoms assessed were related to severity of cough, gastro-esophageal reflux and postnasal drip syndrome.

4.8.1. Symptoms of cough severity

Retching or vomiting while coughing

Retching or vomiting while coughing was also complained by participants in the study. A total of 23 (44.23%) participants at baseline complained of this symptom. Among these, 13 were in placebo arm and 10 in the treatment arm. In total, 12 (23.08%) participants reported moderate to severe symptoms of retching or vomiting. There was no difference at baseline in symptom severity of retching or vomiting while coughing between treatment arms (Z= -0.971, P= 0.331).

Chest tightness or wheezing on coughing

Chest tightness or wheezing on coughing was reported in 32 (61.54%) participants at baseline. 75% (21 of 28) participants in the placebo arm

complained of tightness in chest or wheezing in comparison to the treatment arm where only 45.83% (11 of 24) participants reported the same symptom. The difference between the treatment and placebo arms was significant for the symptom of chest tightness or wheezing on coughing (Z= -2.016, P= 0.044). 21 participants in total complained of moderate to severe symptom, 14 of these in placebo arm and 7 in treatment arm.

Cough while eating

Cough while eating was reported by 24 (46.15%) participants at baseline. In placebo arm, 57.14% (16 of 28) of participants reported cough while eating and 8 (28.57%) of these reported of moderate to severe symptom. In treatment arm, 33.33% (8 of 24) of participants reported any form of cough while eating and 3 (12.5%) of these has moderate to severe symptoms at baseline. Statistically, there was no difference between the two arms at baseline (Z= -1.60, P= 0.110).

Cough with certain foods

Symptom of cough with certain foods was present in 23 (44.23%) participants at baseline. In placebo arm, 57.14% (16 of 28) participants reported any form of symptom and 3 (10.71%) of these reported of moderate to severe symptom. In treatment arm, 29.17% (7 of 24) of participants reported cough with certain foods and 3 (12.5%) of these complained moderate to severe symptoms at baseline. There was no statistical difference between the two arms of study at baseline (Z= -1.35, P= 0.177).

Cough when getting out of bed in morning

73.08% (38 of 52) of the participants at baseline complained of the symptom of cough when getting out of bed in morning. Of these, 20 of 52 (38.46%) at baseline suffered from moderate to severe problem with cough while getting out of bed in morning, 13 were from placebo and 7 from the treatment arm. 71.43% (20 of 28) participants of the placebo arm and 75% (18 of 24) participants of the treatment arm reported of cough while getting out of bed. There was no difference between the study arms in regards to this symptom at baseline (Z= -0.59, P= 0.555).

Cough brought on by speaking or singing

Cough brought on by speaking or singing was reported in any severity by 38 (73.08%) of 52 participants at baseline, 26 of these (50%) suffered from moderate to severe symptom of coughing while speaking or singing. In placebo arm, 21 of 28 (75%) participants reported any kind of cough brought on by speaking or singing and 13 (46.43%) reported moderate to severe symptom. In treatment arm, 17 of 24 (70.83%) participants reported this symptom and 13 (54.17%) of these participants complained of moderate to severe symptom. There was no difference between the study arms (Z= -0.37, P= 0.708) at baseline in terms of symptom severity for cough brought on by speaking or singing.

Coughing more while awake than while asleep

41 of the 52 (78.85%) participants at baseline complained of coughing more while awake than while asleep, 32 of these had moderate to severe symptom. In placebo arm, 23 of 28 (82.14%) participants reported symptoms and 19 complained of moderate to severe symptom of coughing more while awake. In treatment arm, 19 of 24 (79.17%) reported this symptom, while 13 among those reported moderate to severe symptoms. There was no difference between the treatment arms at baseline regarding this symptom (Z= -1.14, P= 0.254).

4.8.2. Symptoms of gastro-esophageal reflux and postnasal drip

Hoarseness

Some kind of hoarseness was reported by 33 of 52 (63.5%) study participants. In the placebo arm, 17 of 28 (60.71%) complained of hoarseness at baseline. 16 of 24 (66.67%) participants in treatment arm complained of some form of hoarseness at baseline. 15 (28.85%) participants in total complained of moderate-severe hoarseness along with HAC. The distribution of symptom severity by treatment arms is presented in table 4-8. On comparing between treatment and placebo arm, there was no significant statistical difference at baseline among treatment arms in symptom severity for hoarseness (Z= -0.07, P= 0.947).

Clearing of throat

Clearing of throat of any severity was complained by39 (75%), of total baseline population, 18 (34.62%) participants reported moderate to severe

symptom. In placebo arm, 82.14% (23 of 28) of the participants reported symptom of clearing their throat, 10 of these with moderate to severe symptom. In treatment arm, 66.67% (16 of 24) of participants reported the symptom with 8 participants having a significant problem (moderate to severe). At baseline, comparison between treatment and placebo arm did not reveal significant statistical differences (Z= -0.47, P= 0.640)

Postnasal drip

Participants complained of some kind of postnasal drip in 26 of 52 (50%) at baseline. Among participants in placebo arm and treatment arm the percentage was 50% for both. In total, 18 (34.62%) participants reported of moderate to severe post nasal drip with HAC at baseline. There was no difference between treatment arms at baseline in terms of symptom severity for postnasal drip (Z= -0.54, P= 0.587).

Cough on lying down or bending over

Cough on lying down or bending over was reported in some form by 39(75%) participants. In placebo arm, 22 of 28 (78.57%) complained of some form of cough on lying down or bending. 17 of 24 (70.83%) in treatment arm reported of this symptom in some form. Participants complaining of moderate to severe symptom were 13 of 52 (25%) at baseline, 10 of these were from placebo arm. There was no difference in symptom severity at baseline between the two treatment arms (Z= -1.904, P= 0.057).

Heartburn, stomach acid or indigestion

18 of 52 (34.62%) participants at baseline complained of heartburn, indigestion or stomach acid. In placebo arm, 10 participants of 28 (35.71%) reported this symptom and in treatment arm 8 of 24 (33.33%) complained. There was no difference between the two arms on comparison (Z= -0.054, P= 0.957). Among the 18 participants with symptom, 12 (66.67%) complained of moderate to severe symptom of heartburn, indigestion or stomach acid and 8 participants reported severe symptoms.

Tickle or lump in throat

Tickle or lump in throat of any severity was present in 34 (65.38%) participants at baseline, with moderate to severe symptoms in 16 (30.77%) participants. In placebo arm, 67.86% (19 of 28) participants reported some sort of tickle or lump in throat and 10 among them reported moderate to severe symptom. In treatment arm, 62.5% (15 of 24) participants reported some sort of tickle or lump in throat and 6 of them reported moderate to severe symptom. There was no statistical difference between the two arms at baseline (Z= -1.163, P= 0.245).

Strange taste in mouth

Strange taste in mouth was complained by 15.38% (8) participants at baseline, 5 from placebo arm and 3 from treatment arm. 5 among these 8 in total had moderate to severe symptoms. There was no difference between placebo and treatment arms (Z= -0.53, P= 0.599).

Table 4-22 Symptom severity distribution at baseline by randomization

Symptoms	Randomization Arm	Symptom Severity					
		No Problem	Little Problem	Mild Problem	Moderate Problem	Big Problem	Severe Problem
Hoarseness	Placebo	11	6	3	3	2	3
	Treatment	8	8	1	4	3	0
Clearing your throat	Placebo	5	9	4	5	3	2
	Treatment	8	3	5	4	3	1
Postnasal Drip	Placebo	14	0	2	7	2	3
	Treatment	12	1	5	3	1	2
Retching or vomiting while coughing	Placebo	15	2	3	1	4	3
	Treatment	14	4	2	4	0	0
Cough on lying down or bending over	Placebo	6	4	8	4	1	5
	Treatment	7	7	7	3	0	0
Chest tightness or wheeze when coughing	Placebo	7	1	6	6	6	2
	Treatment	13	3	1	3	2	2
Heartburn, stomach acid or indigestion	Placebo	18	1	2	1	3	3
	Treatment	16	2	1	0	0	5
Tickle or lump in throat	Placebo	9	1	8	3	2	5
	Treatment	9	5	4	2	3	1
Cough with eating	Placebo	12	3	5	6	2	0
	Treatment	16	0	5	2	1	0
Cough with certain foods	Placebo	12	9	4	2	1	0
	Treatment	17	1	3	1	0	2
Cough when you get out of bed in morning	Placebo	8	4	3	4	4	5
	Treatment	6	1	10	4	2	1
Cough brought on by speaking or singing	Placebo	7	3	5	4	4	5
	Treatment	7	1	3	8	4	1
Coughing more when awake than asleep	Placebo	5	2	1	3	11	5
	Treatment	5	1	5	3	8	2
Strange taste in your mouth	Placebo	23	1	1	1	1	1
	Treatment	21	1	0	1	0	1

Table 4-23 Baseline differences in symptom severity between randomization arms

	Placebo		Treatment			Asymp. Sig.
	Median	IQR	Median	IQR	Z	(2-tailed)
Hoarseness	1	3	1	3	-0.07	0.947
Clearing your throat	1.5	2	2	3	-0.47	0.640
Postnasal Drip	1	3	0.5	2.75	-0.54	0.587
Retching or vomiting while coughing	0	3.75	0	1.75	-0.97	0.331
Cough on lying down or bending over	2	2	1	2	-1.90	0.057
Chest tightness or wheeze when coughing	2.5	3.75	0	3	-2.02	0.044
Heartburn, stomach acid or indigestion	0	2.75	0	1.75	-0.05	0.957
Tickle or lump in throat	2	3.75	1	2.75	-1.16	0.245
Cough with eating	1	3	0	2	-1.60	0.110
Cough with certain foods	1	1.75	0	1.75	-1.35	0.177
Cough when you get out of bed in morning	2	4	2	2.75	-0.59	0.555
Cough brought on by speaking or singing	2	3.75	3	3	-0.37	0.708
Coughing more when awake than asleep	4	3	3	2.75	-1.14	0.254
Strange taste in your mouth	0	0	0	0	-0.53	0.599

4.8.3. Comparison of the symptoms by nationality of the enrollees

To see whether at baseline, being a Nepalese (N=39) or a non-Nepalese (N=13) would make a difference in the reporting of symptom severity, we described the symptom severity frequency and compared the two groups of nationality by non-parametric tests. At baseline, between the two groups, there was difference only in 1 symptom severity in reporting. The symptom cough when you get out of bed in the morning was significantly difference between Nepalese and non-Nepalese participant groups (Z= -2.08, P= 0.037).

Table 4-24 Symptom severity at baseline by nationality of participants

Symptoms	Nationality	Symptom Severity					
		No Problem	Little Problem	Mild Problem	Moderate Problem	Big Problem	Severe Problem
Hoarseness	Nepalese	14	9	4	5	4	3
	Non-Nepalese	5	5	0	2	1	0
Clearing your throat	Nepalese	12	7	5	7	5	3
	Non-Nepalese	1	5	4	2	1	0
Postnasal Drip	Nepalese	21	1	7	4	3	3
	Non-Nepalese	5	0	0	6	0	2
Retching or vomiting while coughing	Nepalese	23	5	4	3	2	2
	Non-Nepalese	6	1	1	2	2	1
Cough on lying down or bending over	Nepalese	7	8	15	6	0	3
	Non-Nepalese	6	3	0	1	1	2
Chest tightness or wheeze when coughing	Nepalese	14	2	6	8	5	4
	Non-Nepalese	6	2	1	1	3	0
Heartburn, stomach acid or indigestion	Nepalese	25	2	2	1	1	8
	Non-Nepalese	9	1	1	0	2	0
Tickle or lump in throat	Nepalese	16	4	8	4	3	4
	Non-Nepalese	2	2	4	1	2	2
Cough with eating	Nepalese	22	3	6	5	3	0
	Non-Nepalese	6	0	4	3	0	0
Cough with certain foods	Nepalese	19	9	5	3	1	2
	Non-Nepalese	10	1	2	0	0	0
Cough when you get out	Nepalese	13	3	10	7	4	2

of bed in morning	Non-Nepalese	1	2	3	1	2	4
Cough brought on by speaking or singing	Nepalese	12	4	4	9	6	4
	Non-Nepalese	2	0	4	3	2	2
Coughing more when awake than asleep	Nepalese	8	1	4	4	16	6
	Non-Nepalese	2	2	2	2	3	1
Strange taste in your mouth	Nepalese	32	2	0	2	1	2
	Non-Nepalese	12	0	1	0	0	0

Table 4-25 Baseline differences in symptom severity by nationality of participants

	Z	Asymp. Sig. (2-tailed)
Hoarseness	-0.72	0.469
Clearing your throat	-0.10	0.923
Postnasal Drip	-1.36	0.173
Retching or vomiting while coughing	-1.12	0.263
Cough on lying down or bending over	-1.21	0.228
Chest tightness or wheeze when coughing	-0.85	0.393
Heartburn, stomach acid or indigestion	-0.65	0.516
Tickle or lump in throat	-1.43	0.154
Cough with eating	-0.58	0.563
Cough with certain foods	-1.73	0.084
Cough when you get out of bed in morning	-2.08	0.037
Cough brought on by speaking or singing	-0.91	0.365
Coughing more when awake than asleep	-1.06	0.291
Strange taste in your mouth	-0.93	0.355

4.9. Symptom checklist at follow up

On analysis of the symptom checklist during follow up, severity of symptoms at follow up were reported and compared between treatment and placebo arms. In addition, change in symptom severity was examined and compared between study arms. Possible association of change in symptom severity with improvement in cough status was examined by Spearman rank correlation in each treatment arm. Association of change in symptom severity score to cough-related quality of life was examined also with Spearman rank correlation coefficient between change in MLCQ score and change in cough related symptom severity.

At follow up, almost all of the symptoms showed a marked reduction in symptom severity, this reduction in agreement with the improvement in cough and a positive mean change in MLCQ score. The symptom severity reduction was marked in both arms of the study.

4.9.1. Symptoms of cough severity

Retching or vomiting while coughing

At follow up, 72.09% (31of 43) of participants did not retch or vomit while coughing, while at baseline, compared to 55.77% at baseline (29 of 52). In placebo arm at follow up, 29.17% (7 of 24) of the participants complained of this symptom and 2 had moderate to severe symptom for retching or vomiting with cough. In treatment arm, 26.32% (5 of 19) participants complained of this symptom and 2 had moderate to severe symptom. There was no statistical difference between the randomization arms at follow up regarding this symptom (Z= -0.16, P= 0.877).

Chest tightness or wheeze when coughing

At follow up, 67.44% (29 of 43) of participants responded that they did not have any tightness or wheezing in chest while coughing, compared to 38.46% (20 of 52) participants at baseline. In placebo arm, 7 (29.17%) of 24 participants at follow up complained of tightness in chest or wheezing while coughing, 2 of these had moderate-severe symptoms. In treatment arm, 7 (36.84%) of 19 participants still had tightness in chest or wheezing while coughing and 4 had moderate to severe symptom. Statistically, there was no difference between the randomization arms at follow up (Z= -0.74, P= 0.462).

Cough while eating

At follow up, 76.74% (33 of 43) participants did not cough while eating compared to 53.85% (28 of 52) participants at baseline. In the placebo arm, 20.83% (5 of 24) participants at follow up reported coughing while eating, none of these reported moderate to severe symptom. In the treatment arm, 26.3% (5 of 19) participants reported cough while eating, 1 of these reported moderate to severe cough. Statistically, there was no difference between the placebo and treatment arm (Z= -0.53, P= 0.596).

Cough with certain foods

At follow up, percentage of participants without any symptom of coughing with certain foods was 73.81% (31 of 42) compared to the baseline 55.77% (29 of 52) participants. In the placebo arm, 26.09% (6 of 23) participants at follow up reported coughing with certain foods, 3 of these reported moderate to severe symptom. In the treatment arm, 26.32% (5 of 19) participants reported cough with certain foods, and 1 of these

reported moderate to severe cough. Statistically, there was no difference at follow up between the placebo and treatment arm (Z= -0.12, P= 0.909).

Cough when getting out of bed in morning

At follow up, 62.79% (27 of 43) percentage of participants reported the symptom of cough while getting out of the bed in the morning, a decrease from the baseline increase from the baseline 73.08% (38of 52). Of these who reported the symptom, 11 suffered from moderate to severe symptom. In placebo arm, out of 24 participants in the arm, 15 (62.5%) complained of cough when getting out of bed in the morning and 5 (20.83%) of them reported moderate to severe symptom. In treatment arm, out of 19 participants in the arm, 12 (63.16%) reported the symptom and 6 complained of moderate to severe symptoms. There was no significant statistical difference between placebo and treatment arms at follow up regarding this symptom (Z= -0.81, P= 0.417).

Cough brought on by speaking or singing

At follow up, 65.12%% (28 of 43) of participants reported the symptom of coughing brought on by speaking or singing as compared to the baseline percentage of 73.08%% (38 of 52). Of these reporting symptom at follow up, 9 suffered from moderate to severe symptoms. In placebo arm, out of 24 participants in the arm, 16 (66.67%) complained of cough while speaking or singing and 4 of them reported moderate to severe symptom. In treatment arm, out of 19 participants in the arm, 12 (63.16%) reported the symptom and 5 complained of moderate to severe symptoms. There was no significant statistical difference between the placebo and treatment arms at follow up regarding cough brought on by speaking or singing (Z= -0.39, P= 0.694).

Coughing more when awake than while asleep

At follow up, 73.81% (31 of 42) of participants reported the symptom of coughing more when awake than while asleep as compared to the baseline percentage of 80.77% (42 of 52). Of those reporting symptoms at follow up, 20 suffered from moderate to severe symptom. In placebo arm, out of 24 participants in the arm, 18 (75%) complained of the symptom and 8 of them reported moderate to severe symptom. In treatment arm, out of 18

participants in the arm, 13 (72.22%) reported the symptom and of these 12 complained of moderate to severe symptoms. There was no difference between the randomization arms at follow up on comparing the symptoms statistically (Z= -1.45, P= 0.147).

4.9.2. Symptoms of cough related to gastro-esophageal reflux and postnasal drip

Hoarseness

At follow up, 67.44% (29 of 43) of the participants reported that they did not suffer from any symptom of hoarseness, a big increase from baseline 36.54% (19 of 52). Of the 14 at follow up who reported hoarseness, 7 suffered from moderate to severe symptoms. At follow up, in the placebo arm, there were 29.17% (7 of 24) of participants with hoarseness, 4 of these had moderate to severe problem with the symptom. In treatment arm, at follow up, 36.84% (7of 19) of the participants had hoarseness, of these, 3 had moderate to severe problem with the symptom. No significant statistical difference was observed at follow up on comparing the treatment arms (Z= -0.47, P= 0.638).

Clearing of throat

At follow up, of the 43 participants followed up, 48.84% (21) reported that they suffered the symptom of clearing throat and 10 of these still had moderate to severe symptoms. This was a big decrease from the baseline value of 75% participants who suffered from clearing the throat. At follow up, in the placebo arm (N=24), there were 11 (45.83%) participants with the symptom of throat clearance, 4 of these had moderate to severe symptom severity. In treatment arm, at follow up (N=19), 10 (52.63%) participants had the symptom and of these, 6 had moderate to severe symptom severity. No significant statistical difference was observed between randomization arms at follow up regarding the symptom clearing your throat (Z= -0.91, P= 0.363).

Postnasal drip

At baseline, 50% of the participants suffered from some form of postnasal drip, and at follow up, only 27.91% (12 of 43), and 4 of these 12 suffered from moderate to severe symptom. At follow up, in the placebo arm (N=24), there were 6 (25%) participants with the post nasal drip, 2 of

these had moderate to severe symptom severity. In treatment arm, at follow up (N=19), 6 (31.58%) participants suffered from postnasal drip and of these, 2 had moderate to severe problem with the symptom. There was no statistical difference between placebo and treatment arms at follow up regarding postnasal drip (Z= -0.62, P= 0.535).

Cough on lying down or bending over

48.84% (21 of 43) of participants at follow up suffered the symptom coughing on lying down or bending over, compared to 75% of the participants at baseline (39 of 52) at baseline. In placebo arm, out of 24 participants in the arm at follow up, 15 (62.5%) complained of coughing on lying down or bending over and 5 of them reported moderate to severe symptom. In treatment arm, out of 19 participants in the arm, 6 (31.58%) reported the symptom and 3 complained of moderate to severe symptoms. No significant difference was observed in statistical comparison of the randomization arms at follow up (Z= -1.63, P= 0.104).

Heartburn, stomach acid or indigestion

At follow up, among 42 responses, 30 (71.43%) responses were 0 (no problem) in the symptom heartburn, stomach acid or indigestion. Among the rest, 5 participants suffered from moderate to severe symptoms even at follow up. To compare, at baseline, 34 (65.38%) participants did not think that the symptom caused any problems. New treatment of acid suppression was not started during the study period. In placebo arm (N=23), 8 (34.78%) complained of this symptom, and 4 had moderate to severe heartburn, stomach acid or indigestion. In treatment arm (N=19), 4 (21.05%) complained of heartburn, stomach acid or indigestion and 1participant suffered from moderate to severe symptoms. At follow up, statistical comparison between placebo and treatment arms did not lead to any significant difference between the arms (Z= -1.14, P= 0.253).

Tickle or lump in throat

At follow up, tickle or lump in throat did not cause any problems in 72.09% (31 of 43) participants at follow up, compared to 18 of 52 (34.62%) at baseline. In placebo arm at follow up (N=24), 8 (33.33%) participants complained of tickle and lump on throat and 2 of these had

moderate to severe symptoms. Similarly, in the treatment arm (N=19), 4 (21.05%) participants reported the symptom, 3 reported that the symptom severity was moderate to severe. Statistically there was no significant difference between placebo and treatment arms at follow up in the symptom severity of tickle or lump in the throat (Z= -0.64, P= 0.525)

Strange taste in mouth

36 of 43 (83.72%) participants at follow up did not report any strange taste in mouth, compared to 44 of 52 (84.61%) at baseline. In placebo arm, out of 24 participants in the arm, 2 (8.33%) complained of strange taste in mouth and none of them reported moderate to severe symptom. In treatment arm, out of 19 participants in the arm, 5 (26.32%) reported the symptom and 2 complained of moderate to severe symptoms. Statistically, no significant difference was observed at follow up between placebo and treatment arms in the symptom strange test in mouth (Z= -1.68, P= 0.094).

Table 4-26Symptom severity in randomization arms at follow up

		No Problem	Little Problem	Mild Problem	Moderate Problem	Big Problem	Severe Problem
Hoarseness	Placebo	17	2	1	3	1	0
	Treatment	12	3	1	1	2	0
Clearing your throat	Placebo	13	5	2	2	2	0
	Treatment	9	2	2	2	3	1
Postnasal Drip	Placebo	18	2	2	2	0	0
	Treatment	13	0	4	1	1	0
Retching or vomiting while coughing	Placebo	17	2	3	1	0	1
	Treatment	14	1	2	2	0	0
Cough on lying down or bending over	Placebo	9	4	6	4	0	1
	Treatment	13	1	2	2	1	0
Chest tightness or wheeze when coughing	Placebo	17	3	2	1	0	1
	Treatment	12	1	2	3	1	0
Heartburn, stomach acid or indigestion	Placebo	15	2	2	2	2	0
	Treatment	15	2	1	1	0	0
Tickle or lump in throat	Placebo	16	6	0	1	1	0
	Treatment	15	1	0	2	1	0
Cough with eating	Placebo	19	3	2	0	0	0
	Treatment	14	2	2	1	0	0
Cough with certain foods	Placebo	17	2	1	2	0	1
	Treatment	14	2	2	1	0	0
Cough when you get out of bed in morning	Placebo	9	6	4	4	1	0
	Treatment	7	1	5	4	1	1
Cough brought on by speaking or singing	Placebo	8	5	7	1	3	0
	Treatment	7	2	5	1	3	1
Coughing more when awake than asleep	Placebo	6	4	6	4	2	2
	Treatment	5	0	1	4	6	2
Strange taste in your mouth	Placebo	22	2	0	0	0	0
	Treatment	14	2	1	0	1	1

Table 4-27 Differences in symptom severity at follow up between treatment and placebo arms

	Z	Asymp. Sig. (2-tailed)
Hoarseness	-0.47	0.638
Clearing your throat	-0.91	0.363
Postnasal Drip	-0.62	0.535
Retching or vomiting while coughing	-0.16	0.877
Cough on lying down or bending over	-1.63	0.104
Chest tightness or wheeze when coughing	-0.74	0.462
Heartburn, stomach acid or indigestion	-1.14	0.253
Tickle or lump in throat	-0.64	0.525
Cough with eating	-0.53	0.596
Cough with certain foods	-0.12	0.909
Cough when you get out of bed in morning	-0.81	0.417
Cough brought on by speaking or singing	-0.39	0.694
Coughing more when awake than asleep	-1.45	0.147
Strange taste in your mouth	-1.68	0.094

4.9.3. Change in symptom severity at follow up

Analysis of how the symptom severity changed over time, between baseline and follow up values, in treatment and placebo arms was explored. Since symptom severity was in a 0-5 response scale, differences in median values were taken to represent the change in symptom severity brought about by treatment regimen.

In the placebo arm, there was no positive change in median scores, 9 of the 14 symptoms showed a negative change in median score from baseline values, reflecting an improvement in the severity of the symptoms. 5 symptoms at follow up showed no change from baseline values.

In the treatment arm, only 3 symptoms showed a negative change in the median values of symptom severity at follow up. Most of the symptoms did not show a median change from baseline values. The summary of the changes is shown in the table 4-27.

Table 4-28 Difference between placebo and treatment arms in the change of symptom severity from baseline

	Z	Asymp. Sig. (2-tailed)
Hoarseness	-0.84	0.400
Clearing your throat	-1.24	0.216
Postnasal Drip	-0.96	0.339
Retching or vomiting while coughing	-0.90	0.371
Cough on lying down or bending over	-0.76	0.445
Chest tightness or wheeze when coughing	-2.09	0.037
Heartburn, stomach acid or indigestion	-0.35	0.729
Tickle or lump in throat	-1.42	0.156
Cough with eating	-1.96	0.050
Cough with certain foods	-0.73	0.465

Cough when you get out of bed in morning	-1.84	0.066
Cough brought on by speaking or singing	-1.08	0.278
Coughing more when awake than asleep	-1.58	0.115
Strange taste in your mouth	-2.44	0.015

On comparing the two randomization arms, a significant difference was seen in between the placebo and treatment arms in the change of symptom severity in 3 symptoms.

The change in symptom severity of chest tightness or wheezing while coughing was significantly different between the placebo and treatment arms (Z= -2.09, P= 0.037). The median change in this symptom from baseline was -2.00 with an IQR of 3 in the placebo arm, while in the treatment arm; the median change in symptom severity was 0.00 with an IQR of 2.

The change in symptom severity of cough with eating was significantly different between placebo and treatment arms (Z= -1.96, P= 0.050). The median change in the symptom severity for the placebo arm was -1.00 with an IQR 2, while in the treatment arm; the change was 0.00 with an IQR of 1.

The other symptom for which the change in severity was significantly different between placebo and treatment arms was strange taste in mouth (Z= -2.44, P= 0.015). Both in the placebo and treatment arms, the median change in symptom severity for strange taste in mouth was 0.00 with an IQR 0.25.

4.9.4. Correlation of change in symptom severity to improvement in cough

In placebo arm of the study, the symptoms explored did not show any correlation between symptom severity and level of improvement in cough apart from cough while speaking or singing (Spearman's rho= -0.51, P= 0.015). In the treatment arm, correlation coefficients were statistically significant. All the significant coefficients were negative, implying that an increase in the level of improvement was reflected by a decrease in the symptom severity. Hoarseness, cough on lying down or bending over, chest tightness or wheezing when coughing, heartburn, stomach acid or indigestion, tickle or lump in throat, cough when getting out of bed in morning, and coughing more when awake than asleep were associated with improvement of cough in the treatment arm.

Change in cough specific quality of life showed a different pattern of correlation. In placebo arm, the statistically significant correlations were seen with symptom of clearing throat; heartburn, stomach acid or indigestion; cough brought on by speaking or singing; and cough more while awake than asleep. All the correlations were negative. In treatment arm, correlation between change in MLCQ score and change in symptom severity were significant with the symptoms coughing on lying down or bending over, chest tightness or wheeze on coughing, heartburn, indigestion or stomach acid, cough with certain foods, and coughing more when awake than asleep.

Table 4-29 Correlation of change in symptom severity to improvement in cough and change in MLCQ score

		Improvement in cough		Change in MLCQ score	
		Placebo (N=22)	Treatment (N=18)	Placebo (N=23)	Treatment (N=16)
Hoarseness	ρ	0.01	**-0.60**	-0.3	-0.39
	P	0.979	**0.008**	0.159	0.131
Clearing your throat	ρ	-0.24	-0.36	**-0.64**	-0.36
	P	0.275	0.147	**0.001**	0.170
Postnasal Drip	ρ	-0.08	-0.4	0.07	0.08
	P	0.718	0.102	0.744	0.781
Retching or vomiting while coughing	ρ	-0.34	-0.46	**-0.44**	-0.27
	P	0.121	0.052	**0.035**	0.310
Cough on lying down or bending over	ρ	-0.30	**-0.81**	-0.14	**-0.62**
	P	0.176	**0.000**	0.53	**0.010**
Chest tightness or wheeze when coughing	ρ	-0.07	**-0.67**	-0.29	**-0.59**
	P	0.744	**0.002**	0.172	**0.016**
Heartburn, stomach acid or indigestion	ρ	-0.34	**-0.59**	**-0.46**	**-0.64**
	P	0.13	**0.010**	**0.031**	**0.008**
Tickle or lump in throat	ρ	-0.2	**-0.49**	-0.33	-0.45
	P	0.381	**0.039**	0.122	0.081
Cough with eating	ρ	-0.02	-0.13	0.07	-0.15
	P	0.931	0.600	0.744	0.591
Cough with certain foods	ρ	0.06	-0.46	0.21	**-0.74**
	P	0.811	0.052	0.33	**0.001**
Cough when you get out of bed in morning	ρ	-0.18	**-0.47**	-0.21	-0.06
	P	0.415	**0.048**	0.343	0.821
Cough brought on by speaking or singing	ρ	-0.38	-0.10	**-0.52**	-0.04
	P	0.082	0.686	**0.012**	0.87
Coughing more when awake than asleep	ρ	-0.16	**-0.70**	**-0.54**	**-0.64**
	P	0.482	**0.002**	**0.008**	**0.010**
Strange taste in your mouth	ρ	-0.01	-0.43	0.23	-0.23
	P	0.967	0.072	0.294	0.399

4.10. Compliance to treatment

Pill count on follow-up was a marker assessed for compliance to treatment. Median pill count was 5.50 with IQR (0-14) and was not

different significantly between the placebo and treatment groups (Z= -0.884, P= 0.376).

5. Discussion

During this study, we for the first time enrolled patients suffering from HAC after ruling out other causes of cough at altitude and examined the effect of an anecdotally successful treatment regimen against placebo. The treatment regimen of salmeterol/fluticasone was been reported by experienced high altitude physicians in successfully treating HAC.

5.1. Improvement in cough

From the data of this study, we found that both placebo and the treatment combination of salmeterol/fluticasone improve HAC at EBC. HAC improved in 34 (85%) subjects at follow up independent of the study arm. Only 6 (15%) of the participants reported no changes in the status of cough at follow up. We showed that the improvement in cough at follow up for combination treatment of salmeterol/fluticasone was not superior to placebo in treatment of HAC at Everest base camp (P= 0.645).

Nationality did not play a role in subjective reporting of improvement of cough at follow up (P= 0.066).

Improvement in cough correlated well with MLCQ score at follow up in both arms. In both arms, the correlations were positive, showing that a better improvement in cough was correlated well with a higher MLCQ score which reflected an improvement in the quality of life. In both placebo arm and treatment arm, correlations were significant at the level 0.000.

Improvement in cough correlated significantly in both arms with change in MLCQ score. A higher change in MLCQ scores meant a better outcome with cough status. We could conclude that the self-reported cough severity used in this study has a good correlation with quality of life measurement with MLCQ. Even in absence of more objective tools, patient reported subjective improvement of cough is a useful tool in cough research.

There was no difference between the arms in significant improvement of HAC at follow up (P= 0.538). The odds of significant improvement in the

treatment arm in comparison to placebo arm were not significant (0.865; [0.246, 3.050]). We concluded that even though the drug combination of salmeterol/fluticasone improve cough in HAC, it is not better than placebo in resulting in such an outcome.

HAC is still a poorly understood phenomenon. There is good evidence that cough threshold is decreased at high altitude even in a controlled hypobaric chamber environment [29]. We know that HAC is an important cause of morbidity at very high altitude, but so far we do not know how to treat it. From earlier trials in cough treatment, we know the existence of physiological effect of placebo apart from true placebo effect causing improvement in cough[77]. During this study, comparing placebo arm effect with a no-treatment arm was not planned. Hence, we could not measure the effect size of placebo on HAC. We have shown that in both treatment and placebo arms, HAC improved significantly. There was an improvement of cough seen in 85% of participants. Patients enrolled in treatment arm even had a worse odds (though not statistically significant) in significantly improving than their counterparts in placebo arm.

Improvement of cough by resolution of early lung edema in sub-clinical HAPE would be supported by the improvement of cough seen in the treatment arm of salmeterol/fluticasone combination. This was a main argument for the anecdotal success of the drug combination. Though we saw a big improvement in cough in treatment arm, the effect of placebo was the same. We cannot make a case for sub-clinical HAPE through our results.

Improvement seen in such a high percentage of cough patients irrespective of the treatment arm can lead to inference that maybe HAC is a self-limiting condition. Previous studies have shown in chamber studies and at altitude that the threshold to cough is lowered in hypobaric hypoxia and subjects suffered from dryness in throat and irritating cough and the cough threshold levels returned to normal values on descent to lower altitude [29, 78]. Natural course of HAC is not described in the literature, with most information being anecdotal; and we cannot say exactly how natural history of HAC has affected our trial results. HAC is typically a self-limiting condition when exposure to the mountains is removed and climbers return to lower altitudes. Anecdotally, and from personal

experiences, patients of HAC complain of cough lasting weeks to months after returning to native altitudes, though the severity decreases with time.

There are no previous treatment- studies in HAC to compare the study results with. The other cough treatment studies are from low altitude, and comparison with these is possible as there as big differences in the tools used, as well as there are significant differences in respiratory physiology at high altitude and pathophysiology of HAC.

5.2. Quality of life measurement

We showed during this study that the MLCQ was a reliable questionnaire that can be employed to assess HAC at high altitude settings (Cronbach's alpha at baseline: 0.816, at follow up: 0.906).There was no difference in response between the Nepalese and non-Nepalese nationalities, thus making it useful for assessing quality of life in across nationalities at EBC.

We did not find any difference on comparing placebo and treatment arms in terms of MLCQ score at follow up, or the change of MLCQ score from baseline. However, comparisons in each arm between baseline and follow up scores revealed a significant difference in each arm. Difference between MLCQ score was follow up and MLCQ score at baseline was positive, indicating that quality of life had increased in both arms after intervention. On analyzing differences in domain scores, we found significant differences in all domains in the placebo arm whereas statistical difference was found only in physical domain in the treatment arm.

5.3. Clinical variables

Heart rate (pulse rate) increases on acute exposure to hypoxia [79, 80]. But on prolonged exposure to altitudes of up to 6000 meters, pulse rate returns to normal values [80]. All the study participants had spent at least 2 weeks at high altitude before being enrolled in the study. Both at baseline and follow up, mean pulse rate in the study population was within normal range for an adult which is 60-100 per minute. In the study participants, pulse rate showed contrasting changes in placebo and treatment arms. Mean pulse rates at follow up decreased in placebo arm compared to baseline mean pulse rate measurements, whereas mean pulse

rate measurements in the treatment group increased at follow up in comparison to baseline values. Though these changes are not significant, this might be due to the salmeterol component of the combination treatment [67].

Oxygen saturation decreases with altitude[81]. Our study participants showed lowered levels of oxygen saturation both at baseline and follow up. The percentage SpO2 measured in our study was not significantly different from measurements in earlier studies at high altitude [23, 82-84]. We did not find a significant change in either of the intervention arms in SpO2 at follow up.

Blood pressures rise on exposure to high altitude and this increase is related to hypoxic ventilator response at altitude [79]. Our data showed a raised SBP and DBP at baseline that fell under the category of 'prehypertension' compared to optimum sea level blood pressure values [85]. At high altitude, there is no established literature on the nature of rise in systemic blood pressure and there are big inter-individual differences. Treatment of all symptomatic hypertension cases and, if asymptomatic, cases with more than 200/120 mmHg is recommended [86]. None of the participants had such levels of blood pressure in our study. SBP and DBP measurements were not significantly different than observed in other studies at high altitude [82, 83, 87]. At follow up, we found that mean DBP in treatment arm was lower than mean DBP at baseline, whereas in placebo mean DBP at follow up was higher than mean DBP at baseline. Though these changes were not significant, a reason for the differing directions of change could be the salmeterol component of the combination treatment [67].

PEF values in placebo during follow up were significantly higher than at enrollment. There was an improvement in PEF seen also in the treatment group at follow up in comparison to baseline measurements but the difference was not significant. Studies on PEF at high altitude have shown a significant increase in comparison to sea level measurements [23, 29]. The improvement in PEF is seen together with the improvement in cough status and MLCQ score at follow up but we cannot with certainty explain the significant increase in placebo PEF values since the measurements

were carried out at the same altitude of EBC in acclimatized climbers. We saw a significant increase in FEV1 in total population at follow up on comparison to baseline measurements but the significance vanishes on analysis of individual arms.

Earlier studies looking at the pulmonary function tests have looked primarily at FVC values and shown that it decreases with altitude. However, some studies have looked at PEF and FEV1 at altitude. These studies have compared differences of the pulmonary functions from sea-level to altitude values. With such comparisons, earlier studies have also ruled out the presence of bronchoconstriction at altitude with the help of beta agonists and oxygen supplementation [23, 29, 69]. PEF and FEV1 mean values, both at baseline and follow up are higher than values defining bronchospasm in a 34 year-old, 170 cm tall Caucasian male [75]. Values for PEF and FEV1 in Indian population are smaller [76, 88], and although one study has found higher FEV1 values in the Nepalese Sherpas in comparison with the European coal and steel (EC&S) FEV1 and FVC data [89], a national standard for pulmonary function does not exist in Nepal.

Our measurements were all carried out at altitude, on participants who were exposed to effects of altitude for at least 2 weeks, and suffering from HAC. We did not measure FVC during this study. Earlier studies at high altitude have shown that FVC reduces significantly at altitude from sea level values but there is no change in FEV1 and PEF rather increases at altitude [29].

We have shown the absence of effect of salmeterol/fluticasone combination treatment in pulmonary function in participants with HAC in comparison to placebo. In our data, PEF in placebo has increased significantly at follow up from baseline values, but not in treatment arm. FEV1 has not increased significantly at all in both arms. There is good evidence that in chronic lung disease, this combination improves FEV1 and PEF [90].In asthma, the drug combination is recommended as anti-inflammatory properties of fluticasone enhances the bronchodilator effect of salmeterol and the beta-agonist action of salmeterol enhances the action of fluticasone through the gluco-corticoid receptors; resulting in a better

overall control of symptoms and improvement of lung function [91]. If bronchoconstriction related to hyperventilation or hypocapnia was present, salmeterol would reverse the condition [56]. In present study, failure of improvement in lung function parameters in the treatment arm makes it difficult to argue for the case of broncho-constriction in being a causal factor for HAC.

5.4. Symptom severity checklist

Post-nasal drip and gastro-esophageal reflux are important causes of cough in low and high altitude [16, 92]. In the present study, the relation of some of the symptoms related to GERD and PND to the improvement of cough and to the change in MLCQ score from baseline values was examined. Other symptoms used to relate the severity of cough were also examined and similar associations studied. For both types of symptoms, we also calculated the change in the severity between baseline measurements and follow up and examined the association of the change to the improvement of cough and the change in quality of life. At follow up, irrespective of the study arm, the symptom severity decreased in participants with improvement in cough. We did not find correlation between any symptom and cough improvement in placebo arm at follow up. The same was true for change in symptom severity from baseline.
In treatment arm, we saw significant negative correlation of improvement in cough with change in severity of symptoms related to GERD/PND (hoarseness, cough on lying down or bending over, heartburn, stomach acid or indigestion, tickle or lump in throat), and symptoms related to cough severity (chest tightness or wheeze when coughing, cough when you get out of bed in morning and coughing more when awake than asleep). With these symptoms, a greater reduction in the symptom severity correlated well with better level of improvement in cough. Similarly, not all symptoms were related with a change in quality of life at follow up. A change in symptom severity of heartburn, stomach acid or indigestion (symptom of GERD), and coughing more when awake than asleep (symptom of severe cough) were significantly related to the change in MLCQ score in both arms. Clearing your throat (symptom of GERD), retching or vomiting while coughing, and cough brought on by speaking

or singing (symptoms of severe cough) were correlated in the placebo arm to the change in MLCQ score. Cough on lying down or bending over (symptom of GERD and severe cough), chest tightness or wheeze when coughing, and cough with certain foods (symptoms of severe cough) were correlated to change in MLCQ score in the treatment arm. All these correlations were negative; a greater reduction in the severity of symptoms was associated with a greater increment in the quality of life score.

Most of the symptoms regressed at follow up in both study arms. Decrease in symptoms of severe cough can be attributed directly to the improvement in cough itself. Decrease in severity of symptoms of GERD is difficult to understand, since the treatment regimen used does not have an effect in reducing acid reflux. Some symptoms of GERD are also common to PND symptoms; hoarseness, clearing throat, and tickle in throat. A reduction in severity of these symptoms could have been brought about by fluticasone.

5.5. Relation of HAC to exercise

At baseline, we saw a difference between placebo and treatment arms in the relation of HAC to exercise. A greater proportion in the placebo responded that HAC was not related to exercise whereas in treatment group, greater percentage of participants responded that exercise makes HAC worse. This difference vanished at follow up and in both arms, most of the participants responded that the cough was not related to exercise. However, there were still 1 in 3 participants at follow up (34.15%) who reported that HAC was made worse by exercise.

5.5. Altitude of HAC occurrence

Altitude-related cough has been explained to occur in two forms by researchers earlier. A type of cough occurring at altitudes below 5000 meters probably due to trauma to respiratory mucosa and a cough occurring above 5000-6000 meters altitude that might me correlated with sub-clinical HAPE has been proposed. The cough from lower altitude persists on descent while the cough developed at the higher altitudes improve on descent [29]. This is the first time we have collected information in the altitude where the HAC occurs for the first time in patients.

In this study, on reporting the altitude where their cough started, most of the climbers participating reported the altitude range 5000-5999 meters which includes the EBC. Second most common altitude of occurrence of HAC was 4000-4999 meters. These responses were preserved on analyzing the study arms or the nationalities of participants responding. HAC, linked with sub-clinical pulmonary edema by earlier researchers, is thought to develop above 5000-6000 meters, which more or less agrees to our findings in the study. We still saw a number of participants developing cough at lower altitudes. During this study, we excluded cough patients who reported symptoms of infection prior to the development of cough.

5.6. Characterization of HAC

Causation of cough is multifactorial. The nature and etiology of cough at altitude is not defined and may cover a number of conditions and etiologies [29]. During the inception of this study, a consensus was developed among high altitude experts and experienced high altitude physicians that HAC is a unique condition and was defined accordingly. From the data gathered in the study, we could add some more characteristics regarding HAC.

With the data at baseline, we can see that a patient of HAC is typically a young climber (mean age 34.42 years), predominantly male (88.46%), without allergies, not using acetazolamide, with a fast ascent profile (mean 6.1 nights from 2800 meters to 5300 meters), without chronic illnesses. HAC patients also had their pulse rate and blood pressure within normal reference range for the altitude of study. In maintaining with the initial definition, patients diagnosed with HAC by high altitude physicians, who agreed to volunteer in the study, had a peripheral oxygen saturation of 83.06±3.84 percentage. We could not, in this study, explain lung function changes in HAC patients between low and high altitude.

5.7. Differences between Nepalese and non-Nepalese climbers

In EBC, we have shown that the Nepalese climbers with HAC are younger than their non-Nepalese counterparts, and took much smaller amount of time to reach the EBC altitude of 5300 meters from point of entry into the Everest region, Lukla (2800 meters). Having the symptom

of breathlessness was distributed with significant difference between the nationalities.

Nepalese climbers had lower mean oxygen saturation than the non-Nepalese climbers. Mean pulse rate among Nepalese climbers was higher than non-Nepalese climbers, though the differences were not statistically significant. Sherpa climbers, adapted to live in high altitude, are descended from Tibetan population. There is evidence that Tibetan high altitude population suffers from lesser altitude stress and has a lower level of oxygen saturation than high altitude populations of other regions of the world [93].

We also found significant differences in PEF between Nepalese and non-Nepalese participants at EBC. Nepalese climbers had a significantly lower PEF than non-Nepalese participants of the population. This can be explained by the stature difference of Nepalese climbers to the non-Nepalese climbers, as is it known that the lung volume which is a function of thoracic dimensions and hence stature, affects PEF [94, 95].

By looking at the baseline characteristics, we can conclude that Nepalese and non-Nepalese participants are different at high altitude. Nepalese population is altitude adapted population, working at high altitude for many years, while the non-Nepalese participants were climbers but not adapted chronically to very high altitudes of the Himalayas. Without proper randomization, the difference in features of these two groups of participants could have had an effect on the results. But we showed that the nationality of participants was well distributed among the study arms and the chances that nationality of participants affecting the results was nullified.

In FEV1, there was a significant difference between male and female climbers at EBC. Though the number of female climbers was low in the study, FEV1 measurements are affected among many other factors, by gender differences [95] which could have resulted in the study conclusions.

5.8. Implications of the study

HAC is still a poorly understood condition troubling not only high mountain climbers but all sojourners to high altitude destinations around

the world. It is a common problem, without a proven treatment, frequently resulting in failed expeditions and decreased quality of life in patients. Though common, we do not yet know the complete natural history of HAC, apart from anecdotal reports and further work is needed to understand this condition.

HAC is a diagnosis of exclusion, but it is extremely difficult at high altitude environment to be able to rule out every other cause of cough. Cough at altitude does not have a uniform nomenclature. It is common for HAC to be labeled as some other kind of cough. There is a necessity to use a uniform diagnosis standard to be used at various high altitude sites around the world. We recommend the use of the definition of HAC used in this study for diagnosis. Hence, a persistent, sometimes paroxysmal cough that disturbs sleep or daily activity or both for more than 1 day in high altitude environment, dry or productive in nature, and not associated with fever, chills, and shortness of breath or desaturation and without significant clinical changes in evaluation of the respiratory and cardiovascular system can be labeled as HAC. Absence of broncho-constriction in lung function test can be used as an additional marker, if available. We cannot support the theory of the role of bronchoconstriction playing in HAC from the results of the present study.

There is clearly a need to study other treatment options in HAC. Additionally, there is a need to study the effects of a placebo treatment with comparisons to a no treatment arm in future studies. We cannot overlook the placebo effect in HAC and future studies must make power and sample calculations taking into account this fact.

Through the results of this study, we have concluded that improvement in cough results in better quality of life and as such, it is important to treat. We have shown that HAC improves with intervention, but no evidence could be shown for treatment regimen we used. Though we cannot support the use of salmeterol/fluticasone combination treatment in HAC, there may be other types of cough at altitude developing due to causes that may respond to this treatment regimen.

Sub-clinical HAPE being a probable cause for HAC was a reason for choosing the treatment combination that has evidence in prevention of HAPE. Though physiologically sound, the theory of sub-clinical HAPE as

a causal factor for HAC is still not proved. The study findings showed that treatment combination with salmeterol, which is a drug for HAPE prevention and acts by enhancing fluid clearance from lungs, was not more effective than placebo. Further studies as to the establishment of sub-clinical HAPE as a causal factor of HAC and treatment options that enhance fluid clearance from lungs in sub-clinical HAPE are needed to support this theory.

Though improvement in the symptoms of GERD/PND has correlated well with improvement in cough and quality of life, further research is needed before a causal relation can be established. Nasoendoscopy and esophageal pH monitoring in patients with cough could provide evidence for GERD/PND. On assessing symptom severities, it would also be helpful in future studies on HAC to see a relation with the reflux severity index (RSI), which is a well validated measure of GERD symptom severity [64]. Of this index, many but not all elements were parts of the symptom checklist used during this study.

5.9. Limitations of study

This study presented some unique limitations to deal with. The study was conducted among Himalayan mountaineers at EBC, and the follow up times for the participants could not be controlled. The terrain, weather high on the mountain and team climbing schedule led to the modification of two follow up points planned initially at week 1 and week 2. Follow up data, finally, was collected at a single point between weeks 1 and 2.
Most climbers with severe symptomatic cough did not participate, citing their plan to use the known salmeterol/fluticasone inhaler rather than risk being placed in a placebo group. The drug combination features regularly in expedition medical kits to very high altitude based on recommendations from high altitude medicine experts. Though this is the first study to gather data on the salmeterol fluticasone combination treatment, it is commonly used in various high altitude areas around the world. This also resulted in 2 participants in changing from the treatment regimen to the commercial drug combination, thus dropping out of the study.
Forced vital capacity (FVC) was not recorded during the spirometry recordings and the standard data for the local population is not available, FEV1 and PEF can only be analyzed against standard data from other regions of the world.

MLCQ has not been used in the mountaineering population previous to this study, hence the results generated from the MLCQ in this study, though strong, have not been verified in other studies yet.
Despite the challenges, this is the only randomized placebo-controlled double blind study to date in the treatment of HAC done at a high altitude site.

6. Conclusion

There is not enough pathophysiological evidence that the HAC is a direct result of sub-clinical HAPE [18, 29] nor is there enough evidence of inflammation in the airways in HAC. In current study, as treatment combination fluticasone and salmeterol failed to show better effect than placebo, we cannot prove the case for sub-clinical HAPE or argue the case of inflammation and bronchoconstriction in HAC although with the results of this study, we cannot rule out these causes with certainty. Our study points to the need of more research into the unique problem of HAC.
There is a distinct lack of literature in HAC, starting from the clinical history and progression of the disease, most work being done is based on experience. There are few studies in the pathophysiology of HAC done in hypobaric chambers. Further studies should address the natural history of HAC. Direct visualization of the upper respiratory tract with endoscopic procedures could give invaluable insight in the causation of HAC. This can be followed by furthering of the pathophysiology studies of HAC, including broncho-alveolar lavage studies to look for markers of inflammation. Treatment studies should be continued to gather evidence for the best treatment for HAC, hence treatment studies also help to accept or reject pathophysiological models. Candidate treatment options in HAC are established antitussives like dextromethorphan and codeine. There is some evidence that acetazolamide inhibits cough reflex, data on HAC is still to be gathered. Studies to establish causation (hypotheses listed in the introduction section) would also point to further treatment trials.

More emphasis in the prevention of HAC should be the goal for high altitude climbing practices. A good acclimatization profile, along with proper hydration and use of moisture retaining buff or balaclavas do help. Hard candies and general cough syrup can provide a sense of relief even though they do not cure HAC. In case of severe cough, descent to a lower altitude could be necessary. In case of well acclimatized climbers, centrally acting antitussives can be tried under supervision of medical personnel acquainted with high altitude medicine. Additionally, based on the results of our study, we cannot support the recommendation to the use of combination treatment of salmeterol/fluticasone in the treatment of HAC.

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Curriculum vitae

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1. Education
   - Center for International Health, Ludwig Maximilian's University, **PhD International Health, Enrolled**
   - Mountain Medicine Society of Nepal, **Diploma in Mountain Medicine, 2011**
   - Institute of Medicine, Tribhuvan University Teaching Hospital, **MBBS, 2010**
2. Experience
   a. Mountain Medicine Society of Nepal**,** Member since 2006
   b. Institute of Medicine, Department of Pediatrics, "International Childhood Tuberculosis Training Workshop", October 2009
   c. Himalayan Rescue Association Nepal
      - Tutor at "Mountain Guides and Porters Training on Mountain Sickness", June 2010
      - Tutor at "Prevention of Acute Mountain Sickness in Pilgrims", July 2010
      - Leader of Himalayan Rescue Association Nepal 'Gosaikunda Pilgrimage Health Camp' **Team** August 2010, August 2011, August 2012
      - Volunteer Physician at Everest ER- Himalayan Rescue Association Everest Base Camp Medical Clinic April-May 2011, April-May 2012
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      - 14. Forum Reisen und Gesundheit Reisen in die Berge in ITB Berlin 2013 'Experiences from Everest', March 2013
   e. Medical Officer at Nepal International Clinic, January 2011- September 2012

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   b. Micro Health Project on Decreasing Pesticide Use in Agriculture for Healthy Living, Panchkhal VDC, Kavrepalanchok, 2003
   c. Study of effects of acute illness, chronic illness, psychiatric disease and disability on Family and Community, 2006
   d. Critical Analysis on Sewage Management in Prithvi Chandra District Hospital, Nawalparasi, 2008
   e. Trend of HIV/AIDS in United Mission Hospital, Palpa- A retrospective Descriptive Study, 2008
   f. Five Year Planning for Japanese Encephalitis Control on Rupandehi District of Nepal, 2008

List of Publications

a. Ellerton J, Milani M, Blancher M, Zen-Ruffinen G, Skaiaa SC, Brink B, **Lohani, Ashish**, Paal, Peter. Managing Moderate and Severe Pain in Mountain Rescue. High altitude medicine & biology. 2014; 15(1):8-14.
b. Paudel D, Abera M, Kyeyune R, Solis-Soto MT, **Lohani A**, Wandiga S, et al. Inequalities in Health: Realities, Efforts and Way Forward. World Medical & Health Policy. 2012; 4(2):1-5.

Appendix

Nepal Health Research Council

Estd. 1991

NHRC

Ref. No. 1047

March 17, 2010

Dr. Buddha Basnyat
Principal Investigator
Nepal International Clinic
Kathmandu, Nepal

Ref: A randomized control trial to ascertain the efficacy of salmeterol 50 meg and fluticasone 250 meg, one puff bid in the treatment of high altitude cough (HAC) on Mount Everest".

Dear Dr. Basnyat,

This is to inform you that NHRC has approved the above mentioned proposal submitted by you. This certifies that there is no ethical objection.

As per NHRC regulation, the investigators have to strictly follow the protocol stipulated in your proposal. Any changes in objective(s), problem statement, research question or hypothesis, methodology, implementation of the research proposal should be approved by the NHRC. Such approval can be obtained after the researcher applies for the modification with the details and justification.

If the research requires transfer of the bio samples to other countries, the investigator should apply to the NHRC for the permission.

Further, the researchers are directed to strictly abide by the National Ethical Guidelines published by NHRC during the implementation of your research proposal. The researcher, as principle investigator is obliged to submit periodic progress report every three months and a copy of the research report with the electronic version. You are requested to submit an article based upon your research in the Journal of Nepal Health Research Council. As per your research proposal, your total research amount is three lakh and NHRC processing fee is NRs. Seven thousand four hundred and forty one.

If you have any question, please contact our research officers.

Thanking you for your kind cooperation.

Sincerely yours,

Dr. Shanker Pratap Singh
Member- Secretary

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UNIVERSITY OF OXFORD

Dr B Basnyat
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24th November 2010

Dear Buddha

Full Title of Study: Treatment of high altitude (HAC) with Salmeterol 50mcg and Fluticasone 250mcg, one puff bid on Mount Everest

OXTREC Reference: 09-10

Thank you for your email 23rd November 2010 requesting an extension to this study to October 2011.

I am happy to be able to take Chairman's action and approve this request.

Yours sincerely,

pp

Dr Richard Mayon-White
OXTREC Chair

Study # _____

High Altitude Cough (Before Intervention)

Cough can be a major problem for people travelling to altitude. It can ruin your climb by limiting exercise, preventing sleep or even causing rib fractures. The questionnaire is completely anonymous and you cannot be identified in anyway from it. Should you agree to complete the questionnaire, please fill it in as accurately and as honestly as possible. Thank you for your help!

Age: …… **M / F Nationality:** ..……..…… **Independent/ Commercial** group (please circle)

Nights from Lukla to EBC: ..... **# days at EBC or above**: ____

Do you have any long term illnesses or take any regular tablets or medicines prescribed by a doctor?

Please give brief details:
……

Are you taking Diamox during this trip? Yes / No If yes, dose: …….

Are you taking any other medications? Yes/No If yes, please list:
Do you have any allergies? Yes/No If yes, please list:

During your time on the trek in or in EBC or above, have you experienced **Breathlessness** (worse than previous altitude experience or compared with others in your group)? (Please circle most appropriate response)
None / Mild / Moderate / Severe/ Incapacitating

Please CIRCLE the response that best applies to you:

a) Have you been troubled by a cough during your time in EBC or above?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

b) Have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

c) Have you been tired because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

d) Have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

e) Have you felt in control of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

f) How often have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the t

g) My cough has made me feel anxious:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

h) My cough has interfered with my ability to exercise, or other daily tasks:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

i) I feel that my cough interferes with the overall enjoyment of my climb:

1	2	3	4	5	6	7

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

j) Exposure to smoke or fumes has made me cough:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

k) My cough has disturbed my sleep:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	Not at all

l) How many times a day have you had coughing bouts?

1	2	3	4	5	6	7
All of the time (continuously)	Most times during the day	Several times during the day	Sometimes during the day	Occasionally through the day	Rarely	Never

m) My cough has made me feel frustrated:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

n) Have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

o) With the cough have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

p) Have you worried that your cough may indicate serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

q) Have you been concerned that other people think something is wrong with you, because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

r) My cough has interrupted conversation:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly at all	Not at all

s) I feel that my cough has annoyed my fellow climbers or tent partner:

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Sometimes when I cough	Occasionally when I cough	Rarely	Never

t) My cough seems to be related to exercise:

1	2	3
Only brought on by exercise	Made worse by exercise	Not related to exercise

u) At what altitude did your cough begin?

1	2	3	4	5	6
1000 – 1999 m	2000 – 2999 m	3000 – 3999 m	4000 – 4999 m	5000 -5999 m	Above 6000 m

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Please CIRCLE the response that best applies to you:

During your time at EBC and climb, how, if at all, did the following problems affect you? (0 = no problem and 5 = severe or frequent problem):

a) Hoarseness or a problem with your voice:	**0**	**1**	**2**	**3**	**4**	**5**
b) Clearing your throat:	**0**	**1**	**2**	**3**	**4**	**5**
c) The feeling of something dripping down the back of your nose or throat:	**0**	**1**	**2**	**3**	**4**	**5**
d) Retching of vomiting when you cough:	**0**	**1**	**2**	**3**	**4**	**5**
e) Cough on first lying down or bending over:	**0**	**1**	**2**	**3**	**4**	**5**
f) Chest tightness of wheeze when coughing:	**0**	**1**	**2**	**3**	**4**	**5**
g) Heartburn, indigestion or stomach acid coming up: **If you take medications for this, please score 5**	**0**	**1**	**2**	**3**	**4**	**5**
h) A tickle in your throat, or a lump in your throat:	**0**	**1**	**2**	**3**	**4**	**5**
i) Cough with eating (during or soon after meals):	**0**	**1**	**2**	**3**	**4**	**5**
j) Cough with certain foods:	**0**	**1**	**2**	**3**	**4**	**5**

k) Cough when you get out of bed in a morning:	**0**	**1**	**2**	**3**	**4**	**5**
l) Cough brought on by speaking or singing:	**0**	**1**	**2**	**3**	**4**	**5**
m) Coughing more when awake than asleep:	**0**	**1**	**2**	**3**	**4**	**5**
n) A strange taste in your mouth:	**0**	**1**	**2**	**3**	**4**	**5**

THANK YOU FOR THE TIME YOU HAVE TAKEN TO COMPLETE THIS QUESTIONNAIRE

The following to be filled out by research staff

OXYGEN Saturation: _____% **Pulse: _____** **Blood Pressure: ____/____**
Peak Flow: _____ **FEV1: _____**

Study # _____

High Altitude Cough (After Intervention)

After the administration of the inhaled medicines given to you at EBC, in general how is your cough now compared to beginning of treatment? (Please circle most appropriate response)

1	2	3	4	5
No Improvement	Improved a bit	Improved moderately	Improved greatly	Completely resolved No cough!

Highest camp reached?

Please CIRCLE the response that best applies to you:

a) Have you been troubled by a cough during your time in EBC or above?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

b) Have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

c) Have you been tired because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

d) Have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

e) Have you felt in control of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

f) How often have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the t

g) My cough has made me feel anxious:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

h) My cough has interfered with my ability to exercise, or other daily tasks:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

i) I feel that my cough interferes with the overall enjoyment of my climb:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

j) Exposure to smoke or fumes has made me cough:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

k) My cough has disturbed my sleep:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	Not at all

l) How many times a day have you had coughing bouts?

1	2	3	4	5	6	7
All of the time (continuously)	Most times during the day	Several times during the day	Sometimes during the day	Occasionally through the day	Rarely	Never

m) My cough has made me feel frustrated:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

n) Have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

o) With the cough have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

p) Have you worried that your cough may indicate serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

q) Have you been concerned that other people think something is wrong with you, because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

r) My cough has interrupted conversation:

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly at all	Not at all

s) I feel that my cough has annoyed my fellow climbers or tent partner:

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Sometimes when I cough	Occasionally when I cough	Rarely	Never

t) My cough seems to be related to exercise:

1	2	3
Only brought on by exercise	Made worse by exercise	Not related to exercise

---

Please CIRCLE the response that best applies to you:

After using the inhaled medcines, did the following problems affect you? (0 = no problem and 5 = severe or frequent problem):

a) Hoarseness or a problem with your voice:	**0**	**1**	**2**	**3**	**4**	**5**
b) Clearing your throat:	**0**	**1**	**2**	**3**	**4**	**5**
c) The feeling of something dripping down the back of your nose or throat:	**0**	**1**	**2**	**3**	**4**	**5**
d) Retching of vomiting when you cough:	**0**	**1**	**2**	**3**	**4**	**5**
e) Cough on first lying down or bending over:	**0**	**1**	**2**	**3**	**4**	**5**
f) Chest tightness of wheeze when coughing:	**0**	**1**	**2**	**3**	**4**	**5**
g) Heartburn, indigestion or stomach acid coming up: If you take medications for this, please score 5	**0**	**1**	**2**	**3**	**4**	**5**
h) A tickle in your throat, or a lump in your throat:	**0**	**1**	**2**	**3**	**4**	**5**
i) Cough with eating (during or soon after meals):	**0**	**1**	**2**	**3**	**4**	**5**
j) Cough with certain foods:	**0**	**1**	**2**	**3**	**4**	**5**
k) Cough when you get out of bed in a morning:	**0**	**1**	**2**	**3**	**4**	**5**
l) Cough brought on by speaking or singing:	**0**	**1**	**2**	**3**	**4**	**5**
m) Coughing more when awake than asleep:	**0**	**1**	**2**	**3**	**4**	**5**
n) A strange taste in your mouth:	**0**	**1**	**2**	**3**	**4**	**5**

THANK YOU FOR THE TIME YOU HAVE TAKEN TO COMPLETE THIS QUESTIONNAIRE

The following to be filled out by research staff

OXYGEN Saturation: _____% **Pulse:** _____ **Blood Pressure:** ____/____

Peak Flow: _____ **FEV1:** _____

CONSENT FORM

High altitude Cough

Principal Investigator: Buddha Basnyat MD - Director, Himalayan Rescue Association.
Nepal International Clinic - GPO BOX 3596, Lal Durbar Marg 47, Kathmandu, Nepal
Ph# 977-1-434 642,435 357

I have read the Patient Information Sheet and understand what will happen in the study. I understand that my participation in this study is completely voluntary and that I may leave the study at any time. There will be no consequences of deciding not to be in the study. All information about me will remain strictly confidential. I can contact the principal investigator at any time if I have concerns or questions about being in the study. His information is at the top of this form.

My signature below indicates that I have read and understand the procedures described in the Patient Information Form and give my informed and voluntary consent to participate in this study. A copy of this form will be given to me for my records.

Participant Name:_____

Signed: _____ Date:_____

Study Staff Name:_____

Signed:_____ Date:_____

Participant Information Sheet

High altitude cough

High altitude cough (HAC), also known as Khumbu cough has been the number one diagnosis for the last 7 years amongst climbers in the Everest Base Camp clinic in Nepal. Cough can be very debilitating at high altitude and can be severe enough to cause a rib fracture. Many factors seem to be involved in causing this cough. At the Everest Base Camp anecdotally over the years the doctors have noticed that an inhaled combination of Salmeterol and Fluticasone has been very effective in the treatment of HAC, but this has never been proven in scientific study.

The main purpose of this research study is to find out if inhaled Salmeterol and Fluticasone will be effective for the treatment of HAC in high altitude climbers. Both Salmeterol and Fluticasone are commonly used drugs for asthma.

This is a randomized trial (RCT); half of the participants receive a placebo and others will receive the study drug. Study groups will be randomly assigned by a computer generated list and neither the participant nor the study administrator will know who received drug or placebo, as this is kept in a secret code, which can be broken by the doctors not associated with the study. RCTs are the most scientific way to determine if drugs (Salmeterol\Fluticasone in this case) work or not for the stated purpose.

All drugs have side effects. The inhaled combination of Salmeterol and Fluticasone is generally considered safe. There may be some coughing with the initial puff in some participants. Some may experience mild throat irritation, palpitations and mild headache. Some participants may have hoarseness and temporary change in voice. Sometimes oral thrush can be a problem and gargling the throat with water after inhalation will help avoid this. A great advantage of these drugs is that they work locally in the lungs and very little is absorbed in the blood stream, so side effects are uncommon.

Benefits for taking part in this study will include specialized counselling about methods of reducing risk of high altitude cough and two free medical evaluations. We are happy to share the results of the study with you if you would like to leave your contact information with the study staff. All information will remain strictly confidential and you are allowed to leave the study at any time if you wish.

Principal Investigator: Buddha Basnyat MD - Director, Himalayan Rescue Association.

Nepal International Clinic - GPO BOX 3596, Lal Durbar Marg 47, Kathmandu, Nepal

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