TREATMENT OF ACUTE MOUNTAIN SICKNESS: IS THE COMBINATION OF ACETAZOLAMIDE AND DEXAMETHASONE BETTER THAN ACETAZOLAMIDE ALONE?

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ABSTRACT

Objective: Acute Mountain Sickness is a common condition encountered at high altitude. Many treatment modalities have been used to treat it, including acetazolamide and dexamethasone. The data regarding any added benefit of combining the two drugs is scarce.

Study Design: Prospective randomized controlled trials.

Place and Duration of Study: To compare the response of patients of Acute Mountain Sickness (AMS) treated with acetazolamide and dexamethasone with those treated with acetazolamide alone.

Material and Methods: A total of 76 consecutive patients of AMS were included in the study at Goma (3300 meters). They were assigned randomly to two groups: group 1 treated with acetazolamide and dexamethasone, and group 2 treated with acetazolamide only. Their progress was noted at 12, 24, 36 and 48 hours.

Results: At 3300 meters, the rate of recovery of patients of AMS treated with Acetazolamide and Dexamethasone was not different from that of those treated with Acetazolamide alone.

Conclusion: The response of patients of AMS treated with acetazolamide and dexamethasone is the same as those treated with acetazolamide alone.

Keywords: Acetazolamide, Altitude, Altitude sickness, Dexamethasone.

INTRODUCTION

Mountaineers and trekkers going to high altitude are subjected to many hazards. They include many health related issues which impede their progress and may even compel them to abort their expedition. As the traveler ascends to high altitude, the atmospheric oxygen pressure gets progressively lower. Less amount of oxygen is available in each breath which may lead to decrease in cerebral perfusion. The mountaineer may, as a consequence, develop a symptom complex characterized by headache, nausea, anorexia and vomiting. This syndrome is known as Acute Mountain Sickness (AMS). AMS is the most common altitude sickness. It may occur at altitude above 2000 meters. It affects up to 40-50% of people travelling to 3000 meters or above. Acute mountain sickness, if left untreated, may get complicated by the development of High Altitude Cerebral Edema (HACE) which is potentially fatal. Keeping this in mind, effort should be put to try to prevent AMS.

AMS can be prevented by adopting a conservative approach to ascent. It is recommended that a person should not ascend more than 300-500 meters in a day. Even then AMS can occur. If that is the case, further climb should be stopped until symptoms improve. AMS can be treated with conservative methods alone or with medicines, depending upon the severity of symptoms. If the individual descends, his symptoms are effectively

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regressed. Reduction in height of 500-1000 m is usually sufficient to abate the symptoms of AMS. If that is not possible, further ascent should at least be stopped till the patient recovers. Supplementary oxygen also improves the symptoms of AMS. Physical exertion should be minimized and simple analgesics like paracetamol taken for headache and antiemetics for nausea and vomiting. Most patients' symptoms resolve within 48 hours on conservative treatment alone.

AMS cannot always be treated with conservative measures alone and drugs have to be used. The diuretic acetazolamide is the commonly used drug for the purpose. It is a carbonic anhydrase inhibitor. It causes increased bicarbonate excretion in the urine. This results in metabolic acidosis and as a consequence, stimulates ventilation. Better ventilation results in better oxygenation. Dexamethasone is the other drug used to treat AMS. Its mechanism of action in high altitude illness is not completely understood.

Although both acetazolamide and dexamethasone are used for treating AMS, it is not established whether their administration as a combination yields any added benefit. This clinical trial was performed to answer this particular question.

**MATERIAL AND METHODS**

These single blind, randomized controlled trials were conducted in Goma Hospital from September, 2010 to March 2011. Goma Hospital is a tertiary care hospital situated at 3300 meters in the Baltistan region in the north of Pakistan. Baltistan is home to Karakoram Mountains and some of the world’s highest peaks. Pakistan army is deployed over a large area of these mountain ranges and maintains its presence all year round. A large number of soldiers are constantly being rotated at high altitude. Therefore, there is constant movement of troops going up to their places of duty at high altitude as well as those coming down from their posts. The soldiers, like all mountaineers, are subjected to altitude-related illnesses. They affect soldiers’ ability to perform at high altitude.

Goma Hospital caters for the medical needs of the soldiers coming from low land areas. These soldiers then ascend to military camps and posts at higher altitude. The inclusion criteria was that only those patients be recruited in the trial who were being exposed to high altitude for the first time and were not suffering from any chronic illness, especially that involving respiratory and cardiovascular systems. It was asked if anyone had been premedicating for prevention of high altitude illness or taking any medicines beforehand. None was found to be doing so. Those patients who were residents of areas above 2000 meters, those who were sick or taking any sort of medicines were excluded.

The permission to carry out the study was sought from the hospital’s ethical committee. Written informed consent was taken from the subjects. All the soldiers were examined and complete medical history was taken. AMS was defined as per the Lake Louise Consensus on the Definition of Altitude Illness as “development of headache plus at least one of: gastrointestinal symptoms (nausea, vomiting or anorexia), insomnia, dizziness and fatigue/weakness, in the setting of recent climb”. Soldiers who fulfilled this criterion and scored 4 or more on the Lake Louise Questionnaire (LLQ) worksheet were declared as cases of AMS. The LLQ worksheet used is shown in fig-1.

The scoring system of LLQ has been studied and validated against the U.S. Army Environmental Symptoms Questionnaire and has demonstrated similar sensitivity and specificity.

The patients were randomly assigned through lottery method to two equal groups: 1 and 2. Group 1 was treated with oral acetazolamide as 250 mg tablets administered eight hourly and intravenous injection...
dexamethasone eight hourly. Group-2 was treated with only oral acetazolamide 250 mg eight hourly. Their progress was noted on LLQ worksheet after every 12 hours till the clinical features subsided.

The mean LLQ score at the start of treatment for the two groups was calculated and compared. The twelve hourly progresses were also compared. Descriptive statistics were used to analyze the results. Independent samples’ t-test/Mann-Whitney U test was applied (where appropriate) to compare quantitative variables between the groups. A p-value less than 0.05 was considered significant.

SPSS version 17.0 was the software used for statistical analysis.

RESULTS

Seventy six soldiers participated in the study. All of them were male. The participants were randomly divided into two equal groups of 38. The age range for group 1 was 21 years to 34 years with mean being 28 years (SD= 3.25) whereas the age range for group 2 was 22 years to 34 years with mean being 27 years (SD= 3). In group 1, the height varied from 1.62 m to 1.9 m, mean being 1.7 m (SD=0.07) and the weight varied from 51 kg to 84 kg, mean being 68 kg (SD= 8.25). The body mass index (BMI) varied from 22 to 26, mean being 23.4 (SD=0.91). In group 2, the minimum height was 1.64 m and maximum was 1.89 m, mean being 1.68m and (SD=0.06 m) while the weight varied from 54 to 82 kg, mean being 66 kg (SD=7 kg). The BMI ranged from 21 to 26, mean being 23 (SD=1.28).

T-tests were conducted and no statistically significant difference was found between the two groups with respect to age (p-value=0.365), height (p-value=0.164), weight (p-value=0.114) and BMI (p-value=0.084).

The comparison between LLQ score of group 1 and group 2 was not statistically significant at any level: baseline, 12 hrs, 24 hrs, 36 hrs, and 48 hrs, as evident in table 1.

DISCUSSION

The study compares the effect of one drug (acetazolamide) with a combination of drugs (acetazolamide and dexamethasone). Thus, two groups were formed for the comparison. A placebo group was deliberately not formed because of the nature of the disease, its potential complications and the remote area where the trial was being performed. Not getting treatment might have put the patients at risk. The safety of the patients comes first, always. Secondly, the purpose of the study was not to establish the efficacy of a drug, which would entail comparing it with a placebo. Acetazolamide is used for the prevention of AMS\textsuperscript{16} as well as its treatment. Acetazolamide resolves the symptoms of AMS and accelerates acclimatization to high altitude\textsuperscript{17}. Dexamethasone, on the other hand, has a more established role in the alleviation of symptoms but less so in acclimatization.

Grissom, et al conducted a randomized double blind trial on 12 subjects with AMS\textsuperscript{18}. They administered acetazolamide to one group and placebo to the other and then observed the

<table>
<thead>
<tr>
<th>Group 1 (n=38)</th>
<th>Group 2 (n=38)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Mean LLQ Score</td>
<td>SD</td>
<td>Mean LLQ Score</td>
</tr>
<tr>
<td>Baseline</td>
<td>5.95</td>
<td>1.541</td>
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<tr>
<td>12 hrs</td>
<td>5.08</td>
<td>1.699</td>
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<td>48 hrs</td>
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effect on symptoms and gas exchange measurements. The result was that acetazolamide administration improved symptoms as well as gas exchange and arterial oxygenation.

Acetazolamide has been hypothesized to act by inhibiting carbonic anhydrase, causing metabolic acidosis and thus prompting the individual to hyperventilate as a compensatory response. The acidosis should take days to develop. However, the patients started recovering within hours of administering the drug. This rapid effect of acetazolamide has been studied in quite a few studies. It has been seen that inhibition of red blood cells and vascular endothelial cell carbonic anhydrase causes carbon dioxide retention almost immediately. Swenson and Hughes studied the effects of acetazolamide one hour after intravenous administration when the time period was insufficient to cause bicarbonate loss through the kidneys. They found significantly raised normoxic ventilation at rest. Montgomery, et al studied the effect of administration of dexamethasone on mountaineers with AMS in a double blind randomized research study in the Rocky Mountains. Administration of dexamethasone resulted in improvement of symptoms of AMS at 2700 meters.

The role of dexamethasone in the treatment of acute mountain sickness was also studied by Levine, et al at a simulated altitude of 3700 m. They put six subjects in a hypobaric chamber and exposed them to the hypobaric hypoxic conditions for 48 hours. AMS was diagnosed with the help of a questionnaire. One group was administered dexamethasone and the other placebo in a randomized, double-blind fashion. The group receiving dexamethasone had 63% improvement of symptoms whereas the placebo group improved only 23%. Dexamethasone did not improve objective physiologic abnormalities like oxygenation, hematologic profile and serum electrolyte levels that occur at high altitude. Thus the role of dexamethasone was established in symptom relief in cases of AMS but not in acclimatization.

We studied the combined effect of acetazolamide and dexamethasone in AMS. This combination has scarcely been studied before for treating AMS. It can help our doctors to administer acetazolamide alone in the patients of AMS.

Some additional data was also gathered in the study. The frequency of clinical features was noted. Amongst them, headache was the most common. Essentially all the cases of AMS complained of it. Headache has been described as the most common clinical feature of AMS in other research studies as well. Millions of visitors to high altitude suffer from headache each year. Fiore et al conducted a study at high altitude and stated that headache was the most common presentation of acute mountain sickness and occurred 6-12 hours after the climb. Headache has been defined as an essential component of AMS due to its prevalence at high altitude.

Headache at high altitude is frequently associated with other clinical features including insomnia and gastrointestinal symptoms of nausea and vomiting. The most common symptoms of AMS in a study on Jade Mountain in Taiwan were headache, followed by insomnia, fatigue or weakness, gastrointestinal symptoms, and dizziness. We also had more or less the same clinical features in our patients. Difficulty in sleeping was the most common symptom after headache, followed by gastrointestinal symptoms including nausea and vomiting.

Neurological features like impairment of judgment and ataxia may occur due to hypoxia. We also noted a couple of subjects with ataxia. We did not see peripheral edema in any patient although Maggiorini et al described peripheral edema as a common sign of AMS.
Treatment of Acute Mountain Sickness

CONCLUSION

The combined administration of acetazolamide and dexamethasone in patients of acute mountain sickness does not improve the rate of recovery when compared to the effect of administration of acetazolamide alone at 3300 meters.

CONFLICT OF INTEREST

The authors of this study reported no conflict of interest.

REFERENCES