Effect of magnesium, high altitude and acute mountain sickness on blood flow velocity in the middle cerebral artery

Christopher LYSAKOWSKI*, Erik VON ELM†, Lionel DUMONT*, Jean-Daniel JUNOD*, Edömer TASSONYI*, Bengt KAYSER‡ and Martin R. TRAMÉR*†

*Neuroanaesthesia Unit, Division of Anaesthesiology, Department of Anaesthesiology, Pharmacology and Surgical Intensive Care, Geneva University Hospitals, Geneva, Switzerland, †Perioperative Evidence-Based Medicine Program, Division of Anaesthesiology, Department of Anaesthesiology, Pharmacology and Surgical Intensive Care, Geneva University Hospitals, Geneva, Switzerland, and ‡Faculty of Medicine, University of Geneva, Geneva, Switzerland

ABSTRACT

Cerebral blood flow is thought to increase at high altitude and in subjects suffering from acute mountain sickness (AMS); however, data from the literature are contentious. Blood flow velocity in the middle cerebral artery (MCAv) may be used as a proxy measure of cerebral blood flow. Using transcranial Doppler sonography, MCAv was measured during normo- and hyper-ventilation in subjects who participated in a trial that tested the effect of magnesium supplementation on the prevention of AMS. First, MCAv was recorded at 353 m (baseline). Subjects were then randomized to receive oral magnesium citrate and matching placebo. A second measurement was taken after a 24 h ascent from 1130 m to 4559 m (altitude I), and a third after a 20–24 h stay at 4559 m (altitude II). Using multivariate linear regression, an association was sought between MCAv and magnesium supplementation, subjects’ age and gender, altitude itself, a temporary stay at altitude, and the presence of AMS (Lake Louise Score > 6 with ataxia, nausea and/or headache). Subjects with AMS had additional Doppler recordings immediately before and after rescue medication (oxygen, dexamethasone and acetazolamide). Forty-seven subjects had measurements at baseline, 39 (21 receiving magnesium and 18 placebo) at altitude I and 26 (13 receiving magnesium and 13 placebo) at altitude II. During hyperventilation, MCAv decreased consistently (for each measurement, \( P < 0.001 \)). Magnesium significantly increased MCAv by 8.4 cm · s\(^{-1}\) (95 % confidence interval, 1.8–15), but did not prevent AMS. No other factors were associated with MCAv. Eleven subjects had severe AMS [median score (range), 11 (8–16)] and, after rescue medication, the median score decreased to 3 (range, 0–5; \( P = 0.001 \)), but MCAv remained unchanged (65 ± 18 cm · s\(^{-1}\) before compared with 67 ± 16 cm · s\(^{-1}\) after rescue medication; \( P = 0.79 \)). MCAv was increased in subjects who received magnesium, but was not affected by exposure to high altitude or by severe AMS.

Key words: acute mountain sickness, acetazolamide, dexamethasone, magnesium, randomized controlled trial, regression analysis, transcranial Doppler.

Abbreviations: AMS, acute mountain sickness; CBF, cerebral blood flow; CI, confidence interval; MCAv, blood flow velocity in the middle cerebral artery; \( \text{SpO}_2 \), capillary oxygen saturation.

Correspondence: Dr Christopher Lysakowski (e-mail christopher.lysakowski@hcuge.ch).
INTRODUCTION

At high altitude, susceptible subjects may develop symptoms of acute mountain sickness (AMS). Acute exposure to high altitude may lead to an increase in brain volume [1]. In subjects who are unable to compensate for this increase in brain volume, for instance through the displacement of cerebrospinal fluid (i.e. the concept of cerebrospinal compliance), intracranial pressure will increase and this may lead to AMS [2]. The underlying pathophysiology of brain swelling is not well understood, but an increase in cerebral blood flow (CBF) induced by hypoxic vasodilatation may be involved [2,3]. Direct measurement of CBF is difficult in field conditions. As a proxy measurement, blood flow velocity in the middle cerebral artery (MCAv), measured by non-invasive transcranial Doppler ultrasonography, has been recommended. Under experimental conditions in healthy volunteers, the agreement between CBF and MCAv is good [4,5]; however, data on the reliability of MCAv as a proxy of CBF during exposure to high altitude are lacking.

Data on MCAv in subjects suffering from AMS are inconsistent. Two studies reported an increase in MCAv in subjects with AMS [6,7]; however, in two other studies, no such association was found [8,9]. To better understand the relationship between AMS and CBF, the impact of high altitude on CBF needs to be clarified. Again, the available data are conflicting. In field studies, exposure to high altitude led to a significant increase in both CBF and MCAv [7,10–12]. In an experimental study in a hypobaric chamber, however, an increase in MCAv could not be confirmed [9].

In this, the second of two papers from a large randomized field study [13], we report on the impact of exposure to high altitude, a 24 h stay at high altitude and AMS on MCAv.

METHODS

Subjects

Subjects who participated in a randomized, placebo-controlled trial that tested the effect of magnesium supplementation on the prevention of AMS were included in this study [13]. The study was approved by our institutional Research Advisory Board and by the Ethical Committee. Written informed consent was obtained from all subjects. Exclusion criteria were residency above 600 m, a stay above 2000 m or any medication during the last 3 months and cardiac, pulmonary, neurological, renal, hepatic or psychiatric disease.

The design of the randomized trial has been described in detail in the accompanying paper [13]. In brief, 70 subjects were randomly allocated to two groups and received either 400 mg of oral magnesium citrate every 8 h or matching placebo. Prophylaxis was started 3 days prior to ascent and was continued throughout the study period until start of descent. On day 1, subjects travelled from Geneva (353 m) to Staffal in the Italian Alps (1130 m), ascended by cable car to 3200 m, and climbed to the Capanna Mantova (3420 m), where they spent the first night. On day 2, they climbed to the Capanna Regina Margherita (4559 m). Time for ascent from 1130 m to 4559 m was 24 ± 2 h in all subjects. Subjects stayed at 4559 m for 48 h.

Doppler ultrasonography

A 2 MHz Doppler probe (TransScan®; Nicolet-EME, Kleinstheim, Germany) was used to measure MCAv and measurements were standardized. All recordings were performed by one of two investigators (C. L. or J.-D.J.). The probe was positioned over the right temporal window for insonation of the main segment of the right middle cerebral artery. If insonation was impossible, the left artery was used. If no temporal window was identified, the subject was not considered for the study. A holder attached to the subject’s head ensured a constant position of the ultrasound probe. Average MCAv was calculated for a fixed recording time of 120 s.

Measurements took place in a calm environment with the subject relaxed in supine position and with both eyes closed. After successful insonation, the subject was asked to breathe quietly for 2 min; this condition reflected normoventilation. End-tidal CO2 (Datex, Helsinki, Finland), measured via an open mouth piece, finger capillary oxygen saturation (SPO2; Datex) and MCAv were recorded during stable normoventilation. Subjects were then asked to double their respiratory rate and to maintain this frequency. This condition reflected hyperventilation. When end-tidal CO2 had dropped by > 1.5 kPa, end-tidal CO2, SPO2 and MCAv values were recorded. It was expected that MCAv would decrease during hyperventilation, due to hypocapnic cerebral vasoconstriction. This would confirm that our setup was able to measure changes in MCAv and, thus, would ensure internal sensitivity of the model. Investigators who performed the Doppler recordings were not blinded to the normo- or hyper-ventilation conditions of the subjects.

The first Doppler measurement was taken in Geneva (353 m) 2–4 weeks before ascent (baseline). At this time point, subjects were recruited for the randomized trial, but were not yet randomized to oral magnesium or placebo [13]. The second measurement was performed 2–4 h after arrival at 4559 m (altitude I) to investigate the impact of high altitude on MCAv. At this time point, subjects had been taking their allocated study treatment (i.e. oral magnesium or placebo) for 4 days [13] to investigate the impact of high altitude on MCAv. A third measurement was performed in the morning after the first night at 4559 m (altitude II) to investigate
the effect of a longer exposure (20–24 h after arrival at 4559 m) to high altitude on MCAv. Throughout the study period, investigators and subjects remained unaware of the allocated oral supplementation [13].

Subjects with severe AMS (defined as a Lake Louise Score > 6 associated with a headache score > 2 and/or a gastrointestinal score > 2 and/or an ataxia score > 2) were randomized further in a treatment trial [13]. The subjects received either a 30 min intravenous infusion of 4 g of magnesium sulphate or matching placebo. In the absence of a significant improvement (defined as a fall in the Lake Louise Score > 50 %) within 30 min of the end of the infusion, they received rescue medication (oxygen by face mask, 4 mg of intravenous dexamethasone and 500 mg of oral acetazolamide) [13]. There was an intention to perform two additional Doppler measurements in these subjects, one immediately before the allocated study treatment was started and one after significant improvement. The aim of these measurements was to test whether MCAv was altered during abruptly changing levels of AMS. Investigators and volunteers were unaware of treatment allocation in the treatment trial; rescue medication, however, was given when required [13].

Statistical analysis
Data on MCAv, \(S_pO_2\) and end-tidal CO\(_2\) were tested for normal distributions. Differences between measurements during normo- and hyper-ventilation were analysed separately in each subset of data (baseline, altitude I and altitude II) using a two-sided Student's \(t\) test for paired data. Normoventilation data were then used for further analyses.

We used multivariate least-square regression analysis to identify independent factors that may be related to MCAv, with MCAv as the response variable. Explanatory variables were high altitude itself, temporary stay at high altitude, Lake Louise Score (as a measurement of the degree of AMS), magnesium supplementation, gender and age. Robust standard errors were chosen to correct for repeated measures. Multivariate regression was performed in a stepwise manner forward and backward; variables were retained in the model if \(P < 0.1\). Since the Lake Louise Score describes symptoms of AMS at altitude but not at baseline, we performed a sensitivity analysis. For one model, Lake Louise Scores for baseline were coded as zero. For the second model, Lake Louise Scores for baseline were coded as missing, and the analysis was restricted to data from altitude I and II.

For severely ill subjects, MCAv values at baseline, before intravenous treatment was started and after rescue medication (i.e. when subjects had significantly improved) were compared using Friedman's test. Lake Louise Scores before the intravenous treatment was commenced and after significant improvement were compared using Wilcoxon's signed-rank test. A \(P\) value < 0.05 was considered significant.

Results
Analysed subjects
Seventy subjects were eligible for the randomized trial [13]; 50 were living near Geneva, and these were invited to take part in the present study. In three of those, a temporal window was not found. Thus 47 subjects had a first measurement at baseline (Figure 1). Of those, 39 (21 receiving oral magnesium citrate and 18 placebo) had a second measurement after arrival at 4559 m (altitude I). Mean (± S.D.) ascent from 1130 m to 4559 m took 24 ± 2 h. Twenty-six subjects (13 receiving magnesium and 13 placebo) had a third measurement after having spent the first night at 4559 m (altitude II); this corresponded to 20–24 h after the second measurement.

Effect of hyperventilation
For each subset of measurements (baseline, altitude I and altitude II), the mean end-tidal CO\(_2\) and MCAv significantly decreased, whereas the mean \(S_pO_2\) significantly increased during hyperventilation compared with normoventilation (Table 1).

Multivariate linear regression
When Lake Louise Scores at baseline were coded as zero, oral magnesium supplementation was significantly and positively associated with MCAv (Table 2a). In subjects receiving magnesium, MCAv was overall increased by 8.4 cm · s\(^{-1}\) [95 % confidence interval (CI), 1.8–15.0] compared with those receiving placebo. None of the other factors reached statistical significance.

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Table 1  Effect of hyperventilation on end-tidal CO$_2$, $\text{SpO}_2$, and MCAv

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type of ventilation</th>
<th>First measurement (baseline, $n = 47$)</th>
<th>Second measurement (altitude I, $n = 39$)</th>
<th>Third measurement (altitude II, $n = 26$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>S.D.</td>
<td>$P$</td>
</tr>
<tr>
<td>End-tidal CO$_2$ (kPa)</td>
<td>Normoventilation</td>
<td>5.2</td>
<td>0.6</td>
<td>$&lt; 0.0001$</td>
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<tr>
<td></td>
<td>Hyperventilation</td>
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<td>0.5</td>
<td></td>
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<tr>
<td>$\text{SpO}_2$ (%)</td>
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<td>97.9</td>
<td>1.0</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Hyperventilation</td>
<td>98.4</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>MCAv (cm · s$^{-1}$)</td>
<td>Normoventilation</td>
<td>60</td>
<td>13</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td></td>
<td>Hyperventilation</td>
<td>38</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Impact of magnesium supplementation, gender and exposure to high altitude on MCAv

In (a), the Lake Louise Score at baseline is coded as zero, with 113 observations ($n = 47$ subjects); $F(3, 46) = 3.81$ (where the number of the numerator and denominator degrees of freedom is given in parentheses), $P = 0.016$, $R^2 = 0.11$. In (b), Lake Louise Score at baseline is coded as missing, with 66 observations ($n = 39$); $F(1, 38) = 9.23$, $P = 0.005$, $R^2 = 0.14$. Two models were used to take into account the fact that at baseline (353 m altitude), volunteers cannot suffer from AMS. Model (a) suggests that with oral magnesium supplementation, MCAv was increased in subjects pre- and post-treatment. In subjects suffering from AMS after the first Doppler measurement at high altitude (Figure 1). In 11 of those, additional Doppler measurements were recorded immediately before intravenous treatment was started according to the randomization scheme (eight receiving intravenous magnesium sulphate and three placebo) [13], and after subsequent relief of symptoms. Before intravenous treatment was started in these 11 subjects, median Lake Louise Score was 11 (range, 8–16; Figure 2). None of the subjects had significant improvement with the study treatment and all needed rescue medication. Within 30 min after rescue medication, the Lake Louise Score had significantly decreased to a median of 3 (range, 0–5; $P = 0.001$ compared with before the start of the intravenous treatment). In the same 11 subjects, mean MCAv at baseline was 64 ± 7 cm · s$^{-1}$, immediately before the intravenous treatment was started was 65 ± 18 cm · s$^{-1}$ and after administration of rescue medication when the Lake Louise Scores had improved by > 50% was 67 ± 16 cm · s$^{-1}$ ($P = 0.73$ for the comparison of all three time points, Friedman’s statistics = 0.605; $P = 0.79$ for the comparison between before intravenous treatment and after rescue medication).

**DISCUSSION**

Subjects suffering from AMS have an increased brain volume [1]. It has been suggested that, among other factors, an increase in CBF may lead to the brain swelling and that this increase in CBF may be due to hypoxic vasodilatation [12,14]. These hypotheses are supported by studies using CBF velocity as a surrogate of CBF [7,15]. However, we were unable to confirm these findings. Even when extreme and abrupt changes in blood flow velocity were expected, i.e. immediately before treatment of severely ill subjects compared with after significant improvement due to successful rescue medication, the Doppler measurements did not indicate any changes in MCAv. There was strong evidence that our Doppler device was able to measure changes in MCAv as, in all subjects, MCAv consistently decreased during hyperventilation, at baseline and at both measurements at high altitude.

**MCAv and Lake Louise Scores in severely ill subjects pre- and post-treatment**

Thirteen subjects developed severe AMS after the first Doppler measurement at high altitude (Figure 1). In 11 of those, additional Doppler measurements were recorded immediately before intravenous treatment was started.
study, 23 subjects reached the same altitude with a similar rate of ascent and MCAv was measured by Doppler. However, repeated Doppler measurements were only taken in 13 subjects. In contrast with our present analysis, there was an increase in MCAv in healthy subjects, which was even more so in subjects who were severely ill. In the present study, we investigated 39 subjects at altitude and, of those, 26 had a further measurement. Length of exposure to high altitude was more than 48 h. To minimize the risk of confounding, we used multivariate linear regression to identify factors that may have an impact on MCAv. Indeed, when controlling for subjects’ age and gender, high altitude itself, temporary stay at altitude, Lake Louise Score and magnesium supplementation, only magnesium was shown to be significantly associated with MCAv. This is in accordance with previous studies reporting a magnesium-related increase in CBF velocity [16,17]. Since magnesium is a physiological calcium antagonist [18], this increase in blood flow velocity may be due to a magnesium-related vasodilatation.

The fact that different studies arrived at different conclusions concerning high altitude and MCAv may be due to different study conditions. In several studies, for instance, exposure to altitude was simulated in a hypobaric chamber [9,15]. These experimental conditions may not adequately reflect the physiopathological changes in the brain of people who are climbing to high altitude, as there is no physical activity and no exposure to changing meteorological conditions. Also, in the hypobaria chamber, rates of ascent are usually much faster than when people are climbing or trekking to high altitude, as it is well known that the risk of developing AMS increases with increasing rates of ascent [19]. In some studies, the final altitude at which the measurements were taken was extremely high. It may be that changes in CBF only occur above a certain altitude. In one study [15], an altitude of 8000 m was simulated and an increase in MCAv was only observed above 5000 m. Finally, in some studies, exposure to altitude was longer than in our present study. For instance, in one trial [20], mean blood flow velocity increased by 20 % after exposure to altitude for 44 h and returned to sea level values after a stay of 4–12 days at altitude. In our present study, exposure to high altitude was shorter. It may be that changes in blood flow velocity are dependent on the length of exposure and, therefore, it could be argued that follow-up was too short in our present study. However, the fact that the length of the follow-up was sufficient to result in a high proportion of patients with severe AMS refutes that argument.

A final question is whether the Doppler device was adequate to study changes in blood flow velocity at high altitude. There are three issues here, namely, correlation of blood flow with blood flow velocity, reliability of the Doppler technique as a screening method to identify true changes in blood flow velocity, and operator skills. First, different indices of CBF have been described. The radioactive xenon technique [12] or positron emission tomography [14] measure blood flow in a given area of the brain. Transcranial Doppler ultrasonography measures blood flow velocity in a well-defined segment of a single artery. This has been widely accepted as a surrogate of CBF, but only under the condition that the diameter of the investigated artery remains unchanged [20]. It has been
shown that the diameter of the middle cerebral artery does not change under conditions of moderate hypoxia or hypercapnia [21]. It is unknown, however, how the diameter of that artery behaves at high altitude and in subjects with severe AMS. Secondly, in patients with vasospasm of the middle cerebral artery after subarachnoidal haemorrhage, Doppler was shown to be an unreliable screening method compared with angiography; sensitivity was only 67% and the negative predictive value was only 78% [22]. This suggested that, in patients who had a vasospasm as diagnosed by angiography, Doppler was unable to confirm this and, if the Doppler did not indicate any change, it was uncertain whether there was any. Extrapolated to the high altitude setting, this would mean that a negative Doppler would not allow, with any confidence, the conclusion that there was no change in blood flow velocity. Finally, it has been shown that operator inexperience with the Doppler device may be associated with false negative results [23]. In view of these numerous potential drawbacks and pitfalls, the use of the Doppler device as a proxy of CBF may be questioned.

In conclusion, we were unable to show any change in MCAv in healthy subjects ascending rapidly to 4559 m. Even in those who were severely ill and who responded favourably to rescue medication, there was no evidence of any change in MCAv and, therefore, MCAv is likely to play little role in AMS. Apart from the well-known effect of hyperventilation, the only factor that was independently associated with a change in MCAv was magnesium supplementation.

ACKNOWLEDGMENTS

We are very grateful to Xavier Carrard and 12 other mountain guides who assured safety of the volunteers throughout the study period, the University of Torino for granting access to the research facilities of the Margharita hut, the Varallo section of the Italian Alpine club and to the guardians of the Margharita hut for their hospitality, and the staff of the Geneva Hospital Pharmacy for the randomization and the study drug preparation. This study was supported by research funds from the Department of Anaesthesiology, Pharmacology and Surgical Intensive Care, Geneva University Hospitals, and the Carlos and Elsie De Reuter Fund, Switzerland. M. R. T. received a PROSPER grant from the Swiss National Science Foundation (No. 3233-501939.97/2).

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Received 27 May 2003/24 September 2003; accepted 22 October 2003
Published as Immediate Publication 22 October 2003, DOI 10.1042/CS20030188