Low haemoglobin levels increase unilateral spatial neglect in acute phase of stroke
Níveis baixos de hemoglobina aumentam a negligência espacial unilateral na fase aguda do acidente vascular cerebral

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ABSTRACT
Objective: The objective of this study was to evaluate the relationship between unilateral spatial neglect (USN) and haemoglobin (Hb) level in acute phase of stroke. Method: Cross-sectional study was performed after right hemisphere ischemic stroke. Independent variable: Hb level (mg/dL); Outcome: USN; Potential confounding factors: Age, National Institutes of Health Stroke Scale (NIHSS), and glycaemia (mg/dL); Characterization variables were obtained from electronic medical records, Hb, mean corpuscular volume (MCV) and glycaemia by laboratory exams, and USN by cancellation and bisection tasks. The relationship between Hb and USN was assessed by Spearman correlation and linear regression model. Results: 40 individuals were evaluated; it was observed that the higher the Hb level, the better the USN test performance, with the two being negatively correlated. There was no significant correlation between VCM level and USN performance. Conclusion: Low hemoglobin levels may indicate a worse performance in USN cancellation and bisection tests in acute phase of stroke.

Keywords: stroke, perceptual disorders, haemoglobins.

RESUMO
Objetivo: O objetivo do estudo foi avaliar a relação entre a negligência espacial unilateral (NEU) e hemoglobina (Hb) na fase aguda do acidente vascular cerebral (AVC). Método: Foi realizado estudo transversal em pacientes com AVC de hemisfério direito dentro das primeiras 48 horas do ictus. Variáveis independentes: nível de Hb (mg/dL); Desfecho: NEU; Fatores potenciais de confundimento: Idade, National Institutes of Health Stroke Scale (NIHSS) e glicemia (mg/dL); A caracterização das variáveis foram obtidas por meio de prontuários eletrônicos, Hb e glicemia por exames laboratoriais, e NEU por meio do Line Cancellation (LCT), Star Cancellation (SCT), e Line Bisection Tasks (LBT). Resultados: 40 indivíduos foram avaliados e foi observado que quanto maior os níveis de Hb, melhor o desempenho nos testes de NEU, demonstrando correlação negativa entre eles. Conclusão: Níveis baixos de hemoglobina podem indicar pior desempenho nos testes de NEU na fase aguda do AVC.

Palavras-chave: acidente vascular cerebral, transtornos da percepção, hemoglobinas.
also contribute to cognitive decline, and that normal haematocrit levels reduce the transfer velocity within cerebral capillaries, improve oxygen extraction by cerebral tissue, and have a positive effect on cortex functions\(^{10,11}\).

In the present study, we evaluated the relationship between Unilateral Spatial Neglect (USN) by means of cognitive with perception tests, haemoglobin (Hb) and mean corpuscular volume (MCV) level in acute phase of stroke. The study hypothesizes that low haemoglobin values are associated with poorer performance on tests of unilateral spatial neglect, given that anaemia may influence the performance of activities that place high demands on the perceptual system, increasing errors on tests of cancelling and bisection of lines.

**METHOD**

This was cross-sectional study of ischemic stroke patients of both sexes presenting with right hemisphere lesion – confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI) – of anterior circulation origin, with defined aetiology, in the acute ictus phase (in the first 48 hours after ictus), under conservative treatment and admitted to the Stroke Unit at Botucatu Medical School University Hospital – *Universidade Estadual Paulista “Júlio de Mesquita Filho”*. Patients were excluded if they presented at least one of the following conditions: haemorrhagic or posterior circulation stroke, left hemisphere ischemia, previous Modified Rankin Scale (mRS)\(\geq 1\), pre-existing dementia, aphasia, visual deficits, other neurological diseases, as were patients who had undergone surgical procedures, thrombolytic treatment, blood transfusion or presented a history of alcohol abuse, hypothyroidism, chronic obstructive pulmonary disease, liver disease, kidney failure or marked leukocytosis on laboratory exams.

**Procedures**

Individuals were evaluated through three USN exams, two for cancellation and one for bisection: a) Cancellations tests: Line Cancellation Task (LCT), scored by lines cancelled in relation to a total number of 40 lines on a sheet of paper\(^{12}\); Star Cancellation Task (SCT), scored by 52 stars cancelled in between distractors\(^{13}\); b) Bisection test: Line Bisection Task (LBT), based on the number of deviations to the right in relation to middle of line marked by patient on each line of the sheet\(^{14}\). In all USN tests the examiner placed the test sheet in front of the patient with the centre of the sheet 50 cm from the glabella, the objective being to measure USN severity.

Hb level (in g/dL), MCV (in fL) and other laboratory exams were performed through a standard protocol by nurses trained in vein puncture to collect blood samples using a sterile technique. The blood sample was collected in a 10 ml tube on the same day that USN tests were applied, and transferred to the clinical laboratory for automated processing. After analysis of the exams, anaemia was defined as Hb<12 g/dL in women and Hb<13 g/dL in men\(^{15}\). The individuals classified as anaemic were divided into microcytic (MCV<80 fL), normocytic (MCV=80-100) or macrocytic (MCV>100 fL)\(^{16}\).

The National Institutes of Health Stroke Scale (NIHSS) and mRS were applied simultaneously with the USN tests to define neurological deficit severity and functional independence; demographic and anthropometric data were obtained from electronic hospital records on the same USN test date.

**Statistical analysis**

The relationship between potential confounding factors (age, sex, neurological deficit severity, functional independence and glycaemia) and USN was assessed by the Spearman correlation and Mann-Whitney test, whereas the relationship between Hb level, MCV and NSU was explored by the Spearman correlation and linear regression model. Significance was set at \(p\) less than .05. Statistical analyses were performed using the software SPSS v.15.0.

**Ethics**

The study was approved by Human Research Ethics Committee of UNESP/Botucatu. All individuals or relatives consented to participate in the study.

**RESULTS**

One hundred and forty consecutive patients with stroke admitted to our University Hospital between June and December 2012, and a total of 40 patients were included in present data. The general demographic data and baseline characteristics are displayed in Table 1, and the potential confounders are presented in Table 2.

Figures 1 and 2 show the negative correlation between Hb and LCT \((r=-0.35; \ p=0.02)\) and SCT \((r=-0.27; \ p=0.09)\). The relationship between Hb level and USN evaluated by LBT (Figure 3) reveals its negative correlation with the number of deviations to the right \((r=-0.36; \ p=0.03)\). These associations were independent of age, sex, neurological deficit, incapacity level or blood glucose.

In the linear regression model, it was demonstrated that the higher the Hb level, the fewer lines and stars were cancelled, with an average of around three lines \((β=-3.1)\) and three stars \((β=-3.2)\) left un-cancelled for each unit increase in Hb (Tables 3 and 4).

Table 5 demonstrates an absence of a statistically significant correlation between the VCM level and the degree of unilateral spatial neglect by means of LCT \((r=-0.089; \ p=0.616)\), SCT \((r=0.001; \ p=0.997)\) and LBT \((r=0.063; \ p=0.723)\).
In our study we found a relationship between Hb level and the presence or absence of USN, and that age, sex, severity (NIHSS), incapacity (mRS) and glycaemia are not confounding factors in the final NSU result. This result is consistent with a physiological mechanism, as the much lower haemoglobin levels reduce cerebral oxygen, and thus worsen USN in the acute phase by establishing a larger area of ischemic penumbra and delimiting the lesion area much earlier. Studies have shown that erythropoietin levels have neuroprotective properties that can regulate some caspases, and therefore prevent neuron death, which is important for reducing the ischemic area and improving neurological deficits.

In the first study where this association was found, a "U" pattern was suggested in the correlation between Hb and USN, where the critical levels, high or low, had determined worse USN. Our results highlight the drop in Hb in the acute phase as a factor of severity and cognitive decline as measured by the USN tests. In an observational study, the authors reported that anaemia in stroke acute phase results in worse functional performance in the first three months.

**Table 1.** Sample description.

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66 (34-87)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>25 (62.5%)</td>
</tr>
<tr>
<td>Race, White</td>
<td>23 (57.5%)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>72.4 (43.8-99.0)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.69 (1.50-1.78)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>23.5 (16.4-38.2)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>5 (3-12)</td>
</tr>
<tr>
<td>mRS</td>
<td>3 (0-4)</td>
</tr>
</tbody>
</table>

**Laboratory Exams**

- Glycaemia, mg/dL: 101.5 (69.0-237.0)
- Urea, mg/dL: 20 (12.0-37.0)
- Creatinine, mg/dL: 0.8 (0.5-1.2)
- Haemoglobin, mg/dL: 14.1 (8.6-16.9)
- MCV, fl: 91.4 (66.9-116.0)

**USN exams**

- Score on LCT: 15.5 (0-36)
- Score on SCT: 33.5 (4-51)
- Score on LBT: 64.4 (14.3-90.9)

*Numbers are mean (SD) or counts (percentages); BMI: Indicates body mass index; mRS: Modified rankin scale; NIHSS: National Institutes of Health Stroke scale; MCV: Mean corpuscular volume; USN: Unilateral spatial neglect; LCT: Line cancellation task; SCT: Star cancellation task; LBT: Line bisection task.

**Table 2.** Relationship between age, neurological deficit and glycaemia as potential confounders for NSU.

<table>
<thead>
<tr>
<th>Variable*</th>
<th>LCT</th>
<th>SCT</th>
<th>LBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.20</td>
<td>0.18</td>
<td>0.19</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.339</td>
<td>0.391</td>
<td>0.375</td>
</tr>
<tr>
<td>mRS</td>
<td>-0.19</td>
<td>-0.22</td>
<td>-0.32</td>
</tr>
<tr>
<td>Glycaemia (mg/dL)</td>
<td>0.402</td>
<td>0.332</td>
<td>0.155</td>
</tr>
</tbody>
</table>

*Numbers are mean (SD) or counts (percentages); (1) p-value associated with Spearman’s correlation; r: estimate of Spearman’s correlation. NIHSS: Indicates National Institutes of Health Stroke Scale; mRS: Modified Rankin scale; LCT: Line cancellation test; SCT: Star cancellation test; LBT: Line bisection test.
Table 3. Linear regression models to explain the number of lines cancelled in LCT as a function of haemoglobin.

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>Standard error</th>
<th>p</th>
<th>CI (l:95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>56.2</td>
<td>15.1</td>
<td>0.001</td>
<td>(24.9-87.4)</td>
</tr>
<tr>
<td>Haemoglobin (mg/dL)</td>
<td>-3.1</td>
<td>1.1</td>
<td>0.010</td>
<td>(-5.4--0.8)</td>
</tr>
</tbody>
</table>

Residual analysis: p=0.591 (Shapiro-Wilk); LCT: Line cancellation task.

Table 4. Linear regression models to explain the number of stars cancelled in SCT as a function of haemoglobin.

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>Standard error</th>
<th>p</th>
<th>CI (l:95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>71.3</td>
<td>17.3</td>
<td>0.001</td>
<td>(35.6-107.0)</td>
</tr>
<tr>
<td>Haemoglobin (mg/dL)</td>
<td>-3.2</td>
<td>1.3</td>
<td>0.018</td>
<td>(-5.9--0.6)</td>
</tr>
</tbody>
</table>

Residual analysis: p=0.829 (Shapiro-Wilk); SCT: Star cancellation task.

Table 5. Correlation between MCV and scores on tests of unilateral spatial neglect.

<table>
<thead>
<tr>
<th></th>
<th>LCT</th>
<th>SCT</th>
<th>LBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCV</td>
<td>r: -0.089</td>
<td>0.001</td>
<td>0.063</td>
</tr>
<tr>
<td>p</td>
<td>0.616</td>
<td>0.997</td>
<td>0.723</td>
</tr>
</tbody>
</table>

MCV: Mean corpuscular volume; LCT: Line cancellation task; SCT: Star cancellation task; LBT: Line bisection task.

and that this relation is associated with increased penumbra area and cerebral infarct7.

Although the Hb level demonstrated an association the all USN tests, it was weakly correlated with LBT, because the latter test has a relatively poor sensitivity for detecting USN. The other tests applied (LCT and SCT) are generally the most sensitive in perceptual disorders18,19. This information is important because the association between Hb and LBT can be influenced by the sensitivity of the test to detect USN.

The results of MCV did not show a statistical correlation with performance on NSU tests. In a descriptive analysis of our data, the patients with macrocytic anaemia presented worse performance on tests of cancelling of lines and stars. This datum has been little explored in the literature, where worsening has been reported only in patients with a deficit in the spatial attention network and cognitive decline in patients with macrocytic anaemia26,21. This finding presents little consistency with our study in which only 4 patients presented macrocytic anaemia.

The limitations of the present study were small sample size, the fact that individuals could have received electrolyte replacement therapy, and other confounding factors, such as tobacco smoking, poor dietary habits or nutrition status. However, our results not only consistently demonstrate a negative association between Hb and USN severity, but also demonstrate the importance of the research objective of establishing ideal haemoglobin levels in the acute phase to avoid cognitive and perceptual decline and improve functional prognosis. We recommend that longitudinal follow-up studies be performed to observe long-term functional outcome and verify whether USN is reduced with haemoglobin replacement.

Based on the results, we conclude that low hemoglobin levels may indicate a worse performance in USN cancellation and bissection tests in acute phase of stroke. Further studies are needed with the inclusion of new confounding factors.

References


