Inefficacy of Piracetam in the Prevention of Painful Crises in Children and Adolescents with Sickle Cell Disease


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Key Words
Piracetam · Pain · Sickle cell disease

Abstract
Analgesia and hydration remain the only safe treatment for painful crises of sickle cell disease; hydroxyurea is effective, but the toxicity is still a problem. Piracetam is a nootropic drug that has reportedly been effective and non-toxic in sickle cell patients, but most studies were not placebo-controlled and included a small number of patients. The present study evaluated the drug in a double-blind crossed placebo-controlled clinical trial in 73 children and adolescents suffering from moderate to severe painful crises for 13 months. Information regarding frequency and severity of pain was acquired through monthly clinical evaluation, visits and house calls, and 4,300 weekly questionnaires filled out by the patients in their domiciles. A monthly pain score was calculated for each patient. Pain was the most frequent adverse manifestation of the disease stressing its significant bio-psycho-social impact. Although nearly all patients and relatives reported a better clinical course throughout the whole study, the drug was ineffective in the prevention of painful crises. This placebo effect may be ascribed to an unplanned and unsystematic 'cognitive-behavioural' management of the children. The pain score in the second semester of the study—both in the experimental and in the control groups—was significantly smaller than that in the first semester. In conclusion, piracetam was found to be ineffective in the prevention of painful crises; a powerful placebo effect due to adequate patient care was demonstrated.

Introduction
Sickle cell disease (SCD) is the most frequent hereditary disturbance in the Afro-descendant population, deserving consideration of the public health system in Brazil and in several other countries. Universal newborn screening introduced since 1998 in the Brazilian state of Minas Gerais [1] revealed a frequency of nearly 1 newborn SCD for every 1,500 live births [2].

SCD progresses with diffuse microvascular occlusion, blood hyperviscosity, exacerbated adherence of blood cells to endothelium, modification of ionic fluxes and cellular hydration, probable hypercoagulability, hyperplasia of the endothelium, vasomotor abnormalities, fat embolism of bone marrow, and thromboembolism [3–5]. Clinical severity is variable and painful crises are very common. Frequency and intensity of pain are probably associated with early mortality [6]. Infections, hemolysis,
dysfunction of multiple organs, and disturbances in physical and emotional development complete the clinical picture [7–9].

Many studies using tens of drugs with potential anti-sickling effects were published, but unconvincing results prevent their widespread use [10, 11]. Hydroxyurea has been effective, but is limited to patients with severe disease, given that the long-term safety mainly in children has not been demonstrated yet [12].

In 1966, Murayama [13] proposed that hydrophobic interactions would be involved in the polymerization of deoxy-HbS and that drugs that would break it could inhibit gelification. Urea was the first to be studied and proved to be effective but with significant toxicity. Similarities between the vaso-occlusive crisis and senile vasculopathy, and between piracetam, a cyclic derivative of γ-aminobutyric acid, and urea led to studies on piracetam in sickle cell disease. Most of the in vitro studies with piracetam, performed mainly during the period of 1974–1992, have shown a reversal of sickling, a reduction in blood viscosity, an increase in erythrocyte elasticity, a reduction in adherence to the vascular endothelium, inhibition of platelet aggregation, water reduction and cell potassium loss [14–19]. An in vitro study performed in 1979 showed the drug to be ineffective [20]. Clinical studies, mainly small and uncontrolled [21], and recently a double-blind placebo-controlled study in 87 children with severe SCD [22] have shown efficacy and lack of toxicity [14, 15, 23–25].

The efficacy of piracetam in preventing the pain of SCD in the few mentioned studies, its excellent tolerability and lack of significant adverse effects motivated the present study in 73 children and adolescents with a history of significant pain.

**Patients and Methods**

The research outline followed Resolution 196/1996 of the Brazilian Health Council and was approved by the Committees of Ethics of the Federal University of Minas Gerais and of the Hemominas Foundation.

The study was performed at Hemominas Foundation, a reference institution in the public network of the state of Minas Gerais, Brazil, for clinical and laboratory follow-up of patients with hemoglobinopathies. The diagnosis of SCD was confirmed by hemoglobin electrophoresis in all cases.

Painful vaso-occlusive crisis was defined as a painful episode in the limbs, vertebral spine, thorax or abdomen, of variable intensity and duration, without other identified cause, with or without medical assistance, preferably recognized by patients and relatives as the characteristic pain caused by the disease. Painful events such as priapism, avascular bone necrosis, osteomyelitis, and acute chest syndrome were not considered crises because of physiological, clinical course and therapeutic specificities.

A pilot study with 65 patients recorded the number and severity of painful episodes for a median period of 11 months; the mean (standard deviation) of the monthly pain score was 2.48 (1.94). Considering α- and β-errors at 0.05 and 0.1, respectively, and assuming that the therapeutic effect of piracetam would be clinically relevant if a reduction of 30% from the value found in the pilot study could be detected, the minimum size of sample should be of 32 children in the placebo and experimental groups. An additional 20% of patients were stipulated for eventual loss of follow-up, resulting in a sample size of 80 patients.

Patients with mild disease were excluded from the experimental phase. Seven patients were considered non-compliant, 6 at the beginning of the study, and were excluded from analysis, leaving 73 patients to be analysed. The pilot study also tested the questionnaires and pain score.

Exclusion criteria were: (1) renal, hepatic, cardiac or coagulation disorders secondary or not to SCD; (2) regular blood transfusion programmes, whatever the indication; (3) use of hydroxyurea; (4) age above 20 or below 5 years; (5) cognitive dysfunction that hindered the report of pain.

Patient age at the beginning of the study ranged from 5 to 20 years (median of 12.1), 33 males (45.2%) and 40 females (54.8%); 42 (57.5%) were Hb SS, 26 (35.5%) Hb SC and 5 (7%) Hb SP+ thalassaemia patients. Mean Z score standardized for weight for age was −0.89 (95% confidence interval −0.66 to −1.12) and that for height for age −0.79 (−0.83 to −1.05). Five patients (6.3%) had undergone splenectomy and 5 (6.3%) cholecystectomy. Acute splenic sequestration had occurred in 12 patients (15%), osteomyelitis in 11 (13.8%), aplastic crisis in 1 (1.3%) and avascular necrosis of femoral head in 4 (5%). Fifty patients (69%) had already been transfused before the study (13 received 1 transfusion, 19 from 2 to 5 and 18 more than 5).

Laboratory tests done prior to the study are in table 1. They were repeated every 3 months in order to screen for side effects. Urinary levels of piracetam were measured at the beginning and then every 3 months throughout the study. A platelet aggregation test was done in 20 children, in the first and second semester of the study.

The clinical trial had a double-blind, placebo-controlled, and cross-over design. Follow-up was done from September 1998 to December 1999. In the first 6 months a randomized half received piracetam whereas the other half received placebo; cross-over was done in the second 6-month period. There was a washout period in between without any drug or placebo: tapering for 2 weeks and without any medication for the remaining 2. Oral piracetam, 4.8 g/m2/day, was given 4 times a day. The active drug was donated by Bioscintica Laboratory, piracetam pills (400 mg each) and placebo were manufactured by Ezequiel Dias Foundation (FUNFD), Health Department of the State of Minas Gerais.

Throughout the study Hemominas Foundation was responsible for the clinical and laboratory management of patients, which was done according to the institutional routine protocol. When in-patient care was necessary, children were admitted mostly at two public hospitals. Physicians were responsible for completing a questionnaire after each monthly appointment for recording and characterizing the painful crises and treatment.

The weekly clinical status was recorded in the questionnaire [26–28], filled out by the patients in their domiciles on Saturdays.

Piracetam in Sickle Cell Disease

Table 1. Laboratory tests immediately before starting the study in 73 patients with SCD

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Diagnosis</th>
<th>n</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin g/dl</td>
<td>SS</td>
<td>42</td>
<td>7.8</td>
<td>3.9-10.2</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>26</td>
<td>10.9</td>
<td>8.9-13.7</td>
</tr>
<tr>
<td></td>
<td>Sβ-thal</td>
<td>5</td>
<td>8.6</td>
<td>7.7-10.1</td>
</tr>
<tr>
<td>Fetal haemoglobin, %</td>
<td>SS</td>
<td>42</td>
<td>6.1</td>
<td>1.0-17.3</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>23*</td>
<td>2.1</td>
<td>0.5-10.0</td>
</tr>
<tr>
<td></td>
<td>Sβ-thal</td>
<td>5</td>
<td>8.9</td>
<td>1.0-14.3</td>
</tr>
<tr>
<td>Reticulocytes, %</td>
<td>SS</td>
<td>42</td>
<td>15.0</td>
<td>0.0-22.0</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>24*</td>
<td>2.0</td>
<td>0.9-8.0</td>
</tr>
<tr>
<td></td>
<td>Sβ-thal</td>
<td>5</td>
<td>3.0</td>
<td>4.4-18.0</td>
</tr>
<tr>
<td>Platelets, x 10^9/l</td>
<td>SS+SC+</td>
<td>73</td>
<td>383.0</td>
<td>142.0-672.0</td>
</tr>
<tr>
<td></td>
<td>Sβ-thal</td>
<td>72*</td>
<td>11.9</td>
<td>3.5-29.7</td>
</tr>
<tr>
<td>Leucocytes, x 10^9/l</td>
<td>SS+SC+</td>
<td>69*</td>
<td>1.3</td>
<td>1.0-1.8</td>
</tr>
<tr>
<td></td>
<td>Sβ-thal</td>
<td>70*</td>
<td>36.5</td>
<td>11.0-117.0</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/l</td>
<td>SS+SC+</td>
<td>70*</td>
<td>15.0</td>
<td>5.0-121.0</td>
</tr>
<tr>
<td></td>
<td>Sβ-thal</td>
<td>70*</td>
<td>210.0</td>
<td>20.0-639.0</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/l</td>
<td>SS+SC+</td>
<td>70*</td>
<td>18.5</td>
<td>3.0-35.0</td>
</tr>
<tr>
<td></td>
<td>Sβ-thal</td>
<td>70*</td>
<td>0.4</td>
<td>0.3-1.1</td>
</tr>
</tbody>
</table>

* Some results are missing.

with or without the collaboration of their guardians. Data collected referred to: (1) general child well-being; (2) frequency, length and description of the painful crises; (3) intensity of the painful crises recorded using an analog-visual scale; (4) pain pinpointing recorded in a body diagram; (5) identification of whether the painful crisis was characteristic of the disease; (6) school or work attendance; (7) impossibility of sleeping, eating, walking, playing, doing outdoor activities, studying, watching television; (8) type of analgesia used and the domiciliary initiatives for pain relief; (9) need for ambulatory medical assistance; (10) need for hospitalization and treatment.

A monthly pain score for each patient was calculated, based on the length and intensity of each episode occurring during the study, according to the following equation:

\[ \Sigma (\text{pain intensity} \times \text{duration of the painful crisis}, \text{in days} \times 30) / \text{period of use of piracetam or placebo, in days} \]

Pain intensity was coded for data analysis as: 0 (absence of pain), 1 (bearable pain) and 2 (unbearable pain) from the record made by the patients in the weekly questionnaires and their report in monthly visits.

A comprehensive approach including home calls encouraged compliance. It was assessed through: (1) subjective impression of the researchers recorded at each visit; (2) percentage of pills missing in relation to the amount the patient was supposed to take in a given period; (3) urinary piracetam analysis done at Ezequiel Dias Foundation laboratory through high performance liquid chromatography. Disclosure of the results was withheld until the end of analysis.

At the end of the study, patients and their relatives answered a questionnaire – separately, to avoid personal influence – that inquired: (1) motivation for study enrollment and the difficulties found throughout; (2) impression of the outcome of the disease in the two semesters of the study; (3) possible pain-inducing factors; (4) impact of the disease on their lives. The final results of the research were disclosed to all patients and relatives.

Results

The 4,300 weekly household questionnaires depicted pain scores ranging from zero to 19.2 (median of 2.0 and mean of 3.1). Fifty-seven patients (78.1%) had scores up to 5, 12 (16.4%) from 5 to 10 and 4 (5.5%) higher than 10. Median pain scores were 3.66, 2.65, and 1.87 for Sβ-thalassaemia (n = 5), SC (n = 26), and SS patients (n = 42). Differences were not statistically significant (p = 0.54).

Levels of pain did not differ significantly when groups were compared. In the first semester of the study medians were 2.51 and 3.03, respectively, for placebo and piracetam (p = 0.46); in the second semester the scores were 1.40 and 1.43, respectively (p = 0.96; fig. 1). Nor were the pain scores significantly different when the piracetam period was compared with the placebo period in the same children (medians of 2.11 and 1.81, respectively; p = 0.11; fig. 2). If only SS patients (n = 42) were analysed, the difference was not significant either (p = 0.46).
Fig. 1. Median of monthly pain scores for children with SCD in the first and second semesters of the study comparing those being given piracetam or placebo.

Fig. 2. Plot scattering of monthly pain score for 73 children with SCD whom sequential piracetam or placebo was given to. Each child is compared with himself/herself.

Fig. 3. Median of monthly pain scores for 73 children with SCD comparing the first and second semesters of study, independently of having been given piracetam or placebo.

The median pain scores for the first and second semesters of the study including all children whether they were taking piracetam or placebo were 2.80 and 1.43, respectively (p = 0.02, fig. 3).

Days of hospitalization during the study ranged from 0 to 42 (median of one); in 93.5% a painful crisis was involved. School absences ranged from 0 to 154 days (median of 10), 92.2% of them due to painful crises. There was no significant difference between the piracetam and placebo periods as to the days of hospitalization (p = 0.87) or school attendance (p = 0.43). 95.6% of the patients and 95.8% of the relatives were convinced that clinical manifestations of the disease during the study period, including painful crises, were much less severe than before.

Compliance with the treatment was 83 and 83.5%, respectively, in each semester of the study, and was considered satisfactory as a whole. Attendance to medical appointments and laboratory tests as well as completion of the questionnaires were fairly good. Compliance of 96 and 89.1% in each semester was established through urinary assays of piracetam.

No clinical or laboratory toxicity of the drug was found. Fourteen patients (19%) received blood transfusion during the study (10 were transfused once, 3 twice and 1 three times). Platelet aggregation curves were normal in 20 patients both during the piracetam and placebo periods.

Discussion

Concurring with the literature, painful crises represented the most frequent adverse manifestation of the disease in the present study [7, 29]. The widely reported high number of painful crises that frequently restrict daily activities of many children was confirmed. Significant levels of school absences and hospitalization were found, and were mostly secondary to the pain. Those findings concur with the literature, particularly with a study that
assessed self-records of 18 children over an average period of 10 months, in which the pain was present 30% of the time and was handled at home in 89% of the cases [30].

Most initial studies with piracetam in SCD were not placebo-controlled, and included a small number of patients; no toxicity that could be attributed to the drug was detected [15, 23–25]. The first report of efficacy was published in 1977 in an uncontrolled study with 12 Brazilian patients to whom piracetam was prescribed for established painful crises, and for the following year as prophylaxis [14]. Significant efficacy of the drug was also reported in a multicentre double-blind, placebo-controlled study, performed in Saudi Arabia on 87 children with severe disease. Clinical severity, number of painful crises, days of hospitalization and transfusion demand decreased significantly when piracetam was given. The clinical effect persisted for at least 6 months after treatment discontinuation. There were no modifications in fetal haemoglobin or in laboratory parameters related to haemolysis and no toxicity was found [22]. Despite adequate sample size and a double-blind placebo-controlled set-up, painful crises were recorded when children were admitted to the emergency room or attended scheduled appointments every 2 or 3 months. Underestimation of painful crises is clearly possible in these situations. Furthermore, there was no cross-over of the drug with placebo rendering impossible comparison between the same patients under different regimens. It should be pointed out however that piracetam or placebo was continuously given for 12 months in contrast to 6 months for each experimental branch in the present study.

Piracetam was not effective in preventing the painful crises in the present study. Measurement biases in the pain score might have been adequately controlled by having patients and relatives recording every painful crisis themselves, including the moderately severe ones that did not require hospitalization and also those which they considered as 'normal' because of low intensity. It is very well known that pain characterization is difficult in chronic diseases. Several studies have stressed that underestimation of pain is very common in studies in which data are acquired only from hospital records instead of also including data recorded by the patients themselves at each painful crisis [4, 7, 8, 27, 30, 31].

Similarly to other studies tackling clinical heterogeneous diseases, one of the main difficulties is the selection of a sample representative of the disease as a whole. The remarkable inter-individual variation of pain scores in patients with SCD requires a large number of patients for a robust analysis. There are, for example, controversial reports on the role of circadian and seasonal factors [4], possibly due to the influence of behavioural changes. Clinical diversity also makes it difficult to define severity scores that require judgement of values in relation to the impact of each complication on the quality of life of each patient [32]. Severity score systems are frequently subjective and arbitrary, being based for instance on the number or length of hospitalization, a parameter clearly subject to arbitrary clinical judgement.

Although piracetam was no better than placebo, 96% of the patients and relatives reported to be convinced of a better pain control throughout the whole study. House staff had the same impression, hence suggesting a strong placebo effect. Interestingly, a lower pain score was demonstrated in the second semester of the study, whether patients were on piracetam or placebo. Seasonal variables probably had no impact, as the semester with lower pain scores corresponded to colder periods, when an increase in the frequency of painful crises of the disease has been reported. It is possible that closer emotional ties involving patients, families and care providers might have had a positive impact on the children's sensation of well-being. The hypothesis that components of an unplanned and unsystematic cognitive-behavioural therapeutic strategy were implicated in the present study is very likely. According to the American Academy of Paediatrics, clinical attitude, family environment, patient and relatives' support and information strongly influence the number and severity of clinical manifestations of SCD in children and adolescents, smoothening the transition to adulthood [33].

Since the physiopathology of the sickling phenomenon is complex, its prevention and treatment will be optimized by a multifactorial therapy [34]. Combining anti-sickling agents with a sympathetic support of patients and families may have a very strong impact on the lives of children with SCD [35]. According to Steinberg [35], 'high technology based approaches will benefit only those few whose families are rich for paying the treatment. For a more far-reaching impact on the majority of children who indeed live in poor and developing countries the approach should be effective, comprehensive and relatively cheap'.

Acknowledgement

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References