Follow-Up of Sickle Cell Disease Patients With Priapism Treated by Hydroxyurea

Sara T.O. Saad,* Camila Lajolo, Simone Gilli, José Francisco C. Marques, Jr., Carmen S. Lima, Fernando F. Costa, and Valder R. Arruda

Hematology and Hemotherapy Center of the State University of Campinas, Campinas, São Paulo, Brazil

Hydroxyurea is one of the most successfully used therapies for sickle cell disease. Results of many clinical trials point to hydroxyurea administration for patients with frequent painful crises and acute chest syndrome. Priapism is one of the complications that could be prevented by hydroxyurea, but there are few reports demonstrating the results. Since November 1993, hydroxyurea has been used in our clinic for preventing priapism in patients with stuttering or major attacks who are still capable of achieving intercourse on demand. Five patients were enrolled in the study, and 4 cases benefited by this treatment. After the initial treatment for the acute attack, all five patients developed stuttering priapism. Hydroxyurea was then introduced at the initial dose of 10 mg/kg, and as the hydroxyurea dosage increased, the number or length of priapism episodes decreased. One to two months after the maximal dose (20–35 mg/kg) was introduced, the episodes disappeared. In two patients, we were forced to administer over 30 mg hydroxyurea/kg to abort the episodes, and, in another patient, 25 mg/kg was necessary. All patients present normal sexual activity. Hydroxyurea was discontinued in two patients, but stuttering priapism reappeared. Hydroxyurea was then re-introduced, and priapism disappeared. One patient, using 20 mg hydroxyurea/kg, had a 6-year remission of priapism after hydroxyurea administration; however, he experienced stuttering priapism, 1 month before a major attack, that progressed to impotence. During that month, he did not seek medical attention. In conclusion, the data here presented suggests that hydroxyurea may prevent priapism attacks in sickle cell disease, probably at higher doses than usually prescribed for painful crisis prevention. Am. J. Hematol. 77:45–49, 2004.

Key words: sickle cell; priapism; hydroxyurea

INTRODUCTION

Sickle cell disease (SCD) is a common hemoglobinopathy that affects 1/1,000 newborns in southeastern Brazil [1] and over 20,000 individuals in Brazil. Sickle cell disease is characterized by multiple-organ infarction following the blockade of capillaries by the interaction of sickle erythrocytes, leukocytes, platelets, and plasma proteins [2–4]. Apparently, no organ is exempted from these changes. Priapism, for example, is another complication resulting from sickle cell, as the corpora cavernosa of the penis are blood reservoirs prone to localized stasis, sickling, and obstruction of venous drainage [5,6]. The prevalence of this complication could be higher than previously described [7,8], as patients do not report short episodes or do not associate the symptoms with sickle disease [9–11], suggesting that better education of these patients is necessary.

The clinical manifestation of priapism appears commonly as stuttering and major attacks [5–7,12,13].

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*Correspondence to: Sara Saad, HemoCentro Campinas, Campinas, São Paulo, Brazil, CEP 13083-970, CP 6198.
E-mail: sara@unicamp.br

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Stuttering priapism usually lasts less than 3 hr and is recurrent, and major attacks exceed 24 hr. Impotence and psychological problems are devastating complications of priapism.

Treatment for acute attacks includes hydration, sedation, aspiration, and irrigation with \(\alpha\)-adrenergic agonist, exchange transfusion \([5,6,14,15]\). Sometimes, aspiration of the corpora or shunt cavernosus-spongiosum becomes necessary; however, most patients progress to impotency, in part because procedures are performed too late \([16,17]\). Success of surgical treatment seems to be related to early treatment (less than 48 hr) \([18,19]\).

Several different strategies have been used in the treatment of recurrent priapism, such as self-administration of etilefrine or phenylephrine and \([14,20–25]\) antiandrogens, but side effects including hypertension, sexual disfunction, etc., are expected. Chronic transfusion has also been reported to be successful for preventing priapism, but allo-immunization, infection, and hemochromatosis are undesirable side effects.

In addition, the efficiency of this treatment is controversial \([26,27]\), and exchange transfusion has been associated with neurologic events \([28–30]\).

Hydroxyurea is one of the most successfully used therapies for sickle cell disease: it elevates levels of fetal hemoglobin (HbF), lowers levels of leukocytes, platelets, and reticulocytes, and consequently reduces endothelial adhesion \([31–34]\). Indeed, hydroxyurea increases red cell hydration and may produce nitric oxide in the plasma of SCD patients following oxidation by heme \([35]\), which also corroborates for a reduction in vasoocclusive events. Results of many clinical trials point to hydroxyurea administration for patients with frequent painful crises and acute chest syndrome. Priapism is one of the complications that could be prevented by hydroxyurea, as suggested by some authors \([5,36]\), but there are few reports demonstrating the results.

Since November 1993, hydroxyurea has been used in our clinic for preventing priapism in patients with stuttering or major attacks who are still capable of achieving intercourse on demand. Five patients were enrolled in the study, and 4 cases benefited from this treatment. We report our experience in treating these patients during the last ten years.

**PATIENTS AND METHODS**

We treated five patients suffering from priapism with hydroxyurea (4 SS, 1 Sb\(0\)), seen at the University of Campinas Hospital, aging from age 13 to 35 years old at the time of the first episode (Table I). The protocol was approved by the Local Ethical Committee, and informed consent was obtained from all patients. Three patients (numbers 2, 3, and 5) were suffering from stuttering priapism, and one of them (patient 5) progressed to major crises 10 months afterward. The other two patients (numbers 1 and 4) presented initially with a major attack successfully treated, but 2 and 3 years after these attacks, respectively, stuttering priapism appeared. Urethritis was probably the cause of the major attack in patient 4, and in the others, no obvious cause was identified.

Initial treatment of all patients included sedation with morphine, oral and intravenous hydration using hypotonic solutions (2–3 vol of 5% dextrose/1 vol of 0.9% NaCl) and sometimes warmth. As these procedures did not result in detumescence during the 4 hr that followed, the patients were submitted to automated or manual red cell exchanges maintaining HbS under 30% and hemoglobin level around 10 g/dL. All but Patient 1 had a transitory resolution of the priapism. None developed cerebrovascular accident. Cavernosa aspiration followed by irrigation with saline and adrenaline was performed on Patient 1, 8 hr after the onset of symptoms and, as this procedure was not successful, shunt cavernosus-spongiosum was also carried out 36 hr after the onset of symptoms. However, a few months or years after this initial episode, all patients experienced stuttering priapism. Table I presents the data of these patients.

**RESULTS**

After the initial treatment of priapism, all five patients developed stuttering priapism. Following our hydroxyurea protocol \([37]\), the initial dose of

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Genotype</th>
<th>Age (years)</th>
<th>Hb (g/dL)</th>
<th>MCV (fL)</th>
<th>HbF (%)</th>
<th>Priapism pattern</th>
<th>Etiology</th>
<th>ET</th>
<th>I/A</th>
<th>Shunt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sb(0)</td>
<td>13</td>
<td>7.8</td>
<td>69</td>
<td>4.5</td>
<td>ST &gt; MC</td>
<td>Unknown</td>
<td>yes</td>
<td>yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>SS</td>
<td>35</td>
<td>7.7</td>
<td>89</td>
<td>2.5</td>
<td>ST</td>
<td>Unknown</td>
<td>no</td>
<td>no</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>SS</td>
<td>20</td>
<td>7.6</td>
<td>82</td>
<td>4.1</td>
<td>ST</td>
<td>Unknown</td>
<td>yes</td>
<td>no</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>SS</td>
<td>16</td>
<td>6.7</td>
<td>91</td>
<td>9.1</td>
<td>ST &gt; MC</td>
<td>urethritis</td>
<td>yes</td>
<td>no</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>SS</td>
<td>17</td>
<td>4.8</td>
<td>97</td>
<td>6.3</td>
<td>ST &gt; MC</td>
<td>Unknown</td>
<td>yes</td>
<td>no</td>
<td>No</td>
</tr>
</tbody>
</table>

*Abbreviations: ET, exchange transfusion; I/A, irrigation with saline and adrenaline; shunt, cavernosus-spongiosum; MC, major crisis; ST, stuttering priapism.*
hydroxyurea was 10 mg/kg/day, given once a day, and was increased by 5 mg/kg/day every 8 weeks until the patient presented no priapism at all. Toxicity was defined by the presence of at least one of the following characteristics: neutrophils < 2 × 10⁹/L, platelets < 100 × 10⁹/L, reticulocytes < 50 × 10⁹/L, a 20% decrease in hemoglobin concentration, a 50% increase in serum creatinine, or a 100% increase in hepatic transaminases (AST and ALT). Patients were seen in the outpatient clinic every 1–2 weeks up to at least 4 months, when they became asymptomatic and the maximal drug dose was reached. After this time, they returned every 8 weeks.

As the hydroxyurea dosage increased, the number or length of priapism episodes decreased. One to 2 months after the maximal dose was introduced (Table II), the episodes disappeared. In two patients, we were forced to administer over 30 mg hydroxyurea/kg to abort the episodes, and in another, the necessary dose was 25 mg/kg. All patients had normal sexual activity, that is, they were capable of achieving intercourse on demand. Before treatment with hydroxyurea, all patients were informed regarding the side effects of the drug, including azoospermia and oligospermia. Semen analysis was not performed regularly unless the patient had the wish or intention of becoming a father. In every visit to the clinic, the patients were seen by one of the three physicians responsible for the hydroxyurea protocol, they were questioned about the presence of priapism attacks or stuttering priapism, and specific files were filled out in order to guarantee the fidelity of all information.

Hydroxyurea was discontinued in two patients due to oligospermia and leg ulcer, respectively. The first (Patient 4) was asymptomatic for 2 years while using 30 mg hydroxyurea/kg; stuttering priapism reappeared 3 months after hydroxyurea discontinuation, and he opted for re-introduction of hydroxyurea despite still presenting oligospermia. The same dose of hydroxyurea that he was using before (30 mg/kg) was prescribed, and the priapism symptoms disappeared 5 weeks afterward. He has been asymptomatic since then (2 years). The last patient (number 3) had been asymptomatic for 3 years using hydroxyurea, but as leg ulcer appeared and healing was difficult, hydroxyurea was discontinued. Stuttering priapism symptoms returned 1 year later, and hydroxyurea was reintroduced. Priapism disappeared 2 months afterward. One year later, the patient was still asymptomatic, without leg ulcers or priapism but decided to discontinue hydroxyurea. Stuttering priapism returned 8 months afterward, and this patient is now under hydroxyurea treatment and is asymptomatic.

Patient 2 had a 6-year remission of priapism after hydroxyurea administration; however, he began to experience stuttering priapism (2–3 times a week lasting less than 30 min), 1 month before a major attack. At that time, he was taking 20 mg hydroxyurea/kg. He did not come to us during the stuttering priapism because he believed that the episodes were not important and could wait until consultation. He came to us during the major attack that lasted 6 hr. He underwent sedation, hydration, and sildenafil treatment [38] without success. He was then submitted to exchange transfusion and cavernosa aspiration followed by irrigation with saline and adrenaline, which was performed 12 hr after the beginning of the symptoms. Finally, 48 hr after the beginning of the symptoms, he had a shunt cavernosus-spongiosum. Doppler analysis revealed very low flow. Complete detumescence occurred 1 month after this episode, and the patient is now impotent.

**DISCUSSION**

Priapism has been recognized as a sickle cell disease complication since 1934 [39], most cases were only reported after 1962. Based on hospital admission data, the prevalence of priapism was estimated in 2–6% [8], but direct questioning revealed that the incidence is higher, reaching 35–38% [7,9]. Conservative and surgical measures have been used for priapism treatment and for preventing new episodes an analogue of gonadotropin-releasing hormone, 47

<table>
<thead>
<tr>
<th>TABLE II. Follow-Up of Patients With Priapism Using Hydroxyurea*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>3</td>
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<tr>
<td>4</td>
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<td>5</td>
</tr>
</tbody>
</table>

*Normal sexual activity, achieve intercourse on demand; ST, stuttering priapism.
thoroughly as possible, about the consequences of every consultation and of informing the patient, as the importance of asking about priapism attacks in the period of 1 month, but he did not seek medical attention, suggesting that this patient was not well-informed about the severity of priapism symptoms. It is important to observe that, in two patients, there was a strong relationship between appearance of priapism symptoms and discontinuation of hydroxyurea and vice-versa. Therefore, we observed that as hydroxyurea dosage increased, the number or length of priapism episodes decreased. Thus, in spite of the fact that priapism occurs in all temporal patterns, including stuttering going into prolonged spells, long spells leading to stuttering, and years between episodes in sickle cell disease, in our patients a clear effect resulting from hydroxyurea administration was observed against the possibility of a random occurrence of fewer episodes of recurrent priapism while receiving this medication.

As described by Al Ja’ma and Al Dabbous [36], the action of hydroxyurea was quickly observed, and there was a relationship between hydroxyurea discontinuation and priapism recrudescence. In that report, the authors used 1.5 g of hydroxyurea. It is possible that this dose could be higher than 25 mg/kg [37]. It is important to observe that, in our patients a clear effect resulting from hydroxyurea administration was observed against the possibility of a random occurrence of fewer episodes of recurrent priapism while receiving this medication.

In conclusion, the data presented here suggest that hydroxyurea may prevent priapism attacks in sickle cell disease, probably at higher doses than usually prescribed for painful crisis prevention.

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