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Outcomes of Hydroxyurea Treatment in Pediatric Sickle Cell Disease Patients with Avascular Necrosis of the Femoral Head: A Case Series

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Abstract— This case series investigated the outcomes of children who received the maximum tolerated dose of hydroxyurea for sickle cell patients with avascular necrosis of the femoral head (AVNFH) at Maternity and Children Hospital, Makkah, Kingdom of Saudi Arabia (KSA) over one year. This retrospective case series report describes four pediatric patients under the age of 14 with sickle cell disease complicated by AVNFH. We excluded all patients who were non-compliant to medication, missed follow-up, started on another modality of treatment, or did not complete laboratory work-up or imaging. Patients were started on the maximum tolerated dose of hydroxyurea, and the assessment was conducted according to clinical manifestations and radiological findings. Our study found significant clinical and radiological improvement in sickle cell patients with AVNFH who took the maximum tolerated dose of hydroxyurea.

Keywords: Sickle cell anemia, sickle cell disease, avascular necrosis of the femur head, hydroxyurea, osteonecrosis

1. Introduction

Sickle cell disease (SCD) is a hereditary blood disorder (with an autosomal recessive pattern) that causes hemoglobin(Hb) alterations that produce hemoglobin S, an abnormal type of hemoglobin (Jastaniah, 2011). This variation results in the frequent occlusion of blood vessels, so patients experience poor development, multiple hospital admissions, and/or organ failure. Consequently, the diseases characterized by high morbidity and mortality, and its sufferers are repeatedly admitted to the hospital due to sudden bone or joint pain episodes as well as acute osteomyelitis and chronic disorders of the joints and bones (avascular osteonecrosis) (Alotaibi, 2017; Arlet et al., 2013).

One of the major complications of SCD is avascular necrosis of the femoral head (AVNFH), a specific form of osteonecrosis driven by bone ischemia that disrupts healthy bone remodeling (Worrall et al., 2016). This can be caused by diverse mechanisms, such as bone fracture or dislocation, intravascular occlusion due to thrombi or embolism, and intraosseous extravascular compression from lipocyte hypertrophy (Shah et al., 2015).

The prevalence of SCD in Saudi Arabia varies by locale. It is highest in the Eastern Region, followed by the southwest, and is estimated to be as high as 2.6% in some places (Jastaniah, 2011). The prevalence of homozygous sickle cell(SS) with AVNFH ranges from 24.6% to 32% at King Faisal Specialist Hospital and Research Center while it is reported as 21.7% in a study on the clinical manifestations and consequences of sickle cell anemia conducted in a tertiary center at King Abdulaziz Medical City, Riyadh (Alhumaid et al., 2018; Padmos et al., 1995).

Hydroxyurea (HU), approved by the food and drug administration in December 2017, has a significant effect in mitigating the painful crises of SCD, such as vaso-occlusive crisis (VOC), acute chest syndrome, and the transfusions required by the increased production of fetal hemoglobin, which can produce nitric oxide (Gladwin et al., 2002). In Adekile et al.'s study conducted in Kuwait, the prevalence and rate of progression of AVNFH were considerably lower than those previously reported

for patients not treated with HU, and the authors found that HU treatment does not appear to be a risk factor for AVNFH. It has the potential to prevent new lesions while also slowing the development of existing AVNFH (Adekile et al., 2019). Mahadeo reported in a 2011 study, however, that SCD patients exposed to HU were three times more likely to experience AVN than those not exposed to the drug (Kris M Mahadeo et al., 2011; Kris Michael Mahadeo et al., 2008).

In light of these conflicting data on HU's efficacy in preventing AVN secondary to sickle cell anemia (SCA) and due to the scarcity of published data on this topic in our region, we will devise a study to follow a number of patients after a trial of HU to monitor its efficacy in preventing the complications mentioned above. This could help add useful scientific information to the existing pool of data and will help and guide us in our future guidelines and policymaking in these patients.

The study investigated the outcomes of SCD patients with AVNFH after receiving the maximum tolerated dose (MTD) of HU at Maternity and Children Hospital (MCH) in Makkah for one year.

2. Patients and methods

This case series study describes four patients under the age of 14 with SCD complicated by AVNFH who presented to the Maternity and Children Hospital in Makkah. A guardian or one parent of each participating child provided written consent after being told the benefits, expected risks, and side effects of the medication. The exclusion criteria included children who had reached adulthood, were noncompliant to medication, missed follow-up, started another treatment modality, or did not complete laboratory work-up or imaging.

We assessed the patients clinically by pain score and limping status and took bilateral hip X-rays and MRIs on the basis of the Steinberg staging system. The assessment was carried out before and after starting the MTD of hydroxyurea. The participants were followed up regularly as outpatients for any other complications or drug side effects during the study period (See Figure 1).

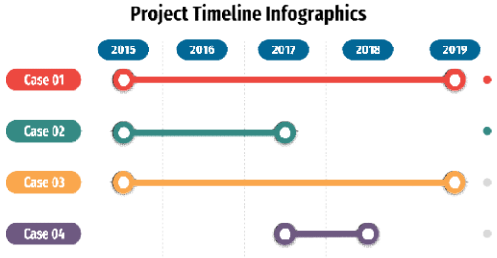
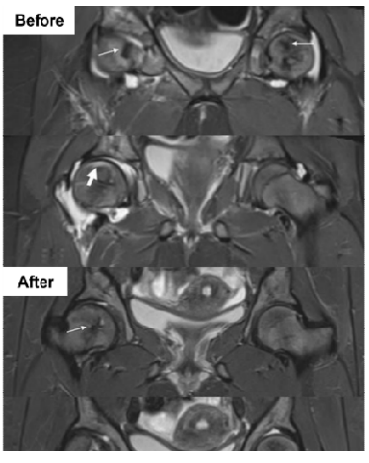


Figure 1

We used a data collection sheet to record patient demographics, such as age, sex, therapeutic agents used, as well as other treatments, such as folic acid, if provided. Details of the presentation of AVNFH were also documented, along with radiologic images and the results of the initial laboratory tests, including hemoglobin level, platelet count, mean corpuscular volume (MCV), neutrophil count, and hemoglobin electrophoresis. Any change in the severity of the AVNFH symptoms and progression, including complete resolution after initiating the MTD of hydroxyurea, was also documented. The patient data were preserved in the hospital record, as it is part of the patient medical record.The ethics committee Institutional Review Board ,Makkah approved the research (code H-02-K076-1120-401).



2.1 Case 1

A Saudi girl was diagnosed with SCD as a one-year-old, as her initial Hb electrophoresis was HbS = 97.08%, HbA2 = 2.92%, and HbF = 8.1%. The

patient was on folic acid and a low dose of HU (500 mg twice weekly) with good compliance. Of her 13 siblings, two had sickle cell anemia.

In March 2015, she presented to the emergency room at age 11, complaining of a sudden onset of right hip pain for one day, which was progressive, radiated to the right thigh, knee, and leg, and was not relieved by analgesic. The pain was associated with lower back pain. She had no history of major trauma. A clinical examination revealed limping and moderate tenderness in the right leg but no swelling, redness, fever, or shortening of the limb. Her pain score was 10 out of 10.

A laboratory investigation revealed hemoglobin of 7.1 g\dL (11–16 g\dL), MCV of 79.7 FI (77–93 FI), neutrophils of 2.17 10^3\UI (2–10 10^3\UI), and platelets of 237 10^3\UI (170–490 10^3\UI) (see Table 1). The radiological findings included an MRI that showed bilateral femoral head focal sclerosis, right subchondral high signal line, and bilateral effusion (greater on the right side).

The patient was managed with the MTD of HU 20 mg kg d; 1,000 mg/od and followed up for four years with good improvement clinically and radiologically. In January 2019, an examination revealed improvement in clinical manifestations (decreased pain and limping). A laboratory investigation found hemoglobin of 10 g\dL (11–16 g\dL), MCV of 104 FI (77–93 FI), neutrophils of 1.4 10^3\UI (2–10 10^3\UI), and platelets of 261.0 10^3\UI (170–490 10^3\UI). Radiological evaluation by MRI revealed an abnormal signal intensity in the right femoral head and subtle sclerosis in the left femoral head. Bilateral AVNFH and joint spaces were preserved. Although the signal change in the right femoral head was greater than the baseline MRI, it was at the same stage "stage 2" (See Figure 2).

2.2 Case 2

A Saudi girl was diagnosed with sickle cell anemia at the age of 8 months, as her initial Hb electrophoresis was HbS = 84.6%, HbA2 = 3.9%, and HbF = 8.5%. She was on folic acid and exhibited good compliance to HU 500 mg 3×/week, prescribed when she was two years old. The patient had multiple attacks of VOC every two months and a history of blood transfusion before one year. There was a positive family history of sickle cell anemia (her father was affected, and her siblings were carriers of SCA). She had no history of fever or major trauma.

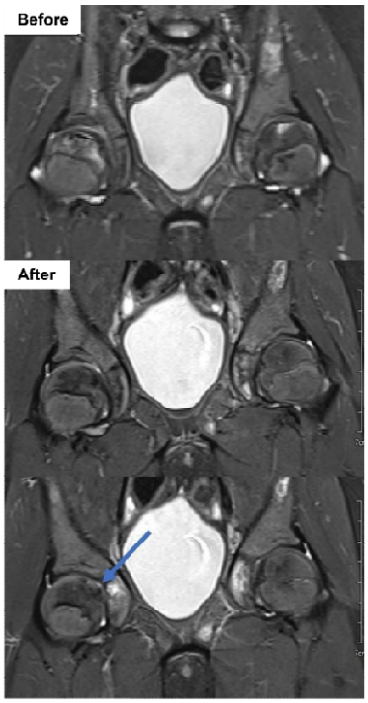


Figure 3. Case 2

In September 2015, she presented to the emergency room at age 11 years with a sudden onset of right hip pain for one day, initially in the right thigh, progressive, and radiating only to the back. The pain, severe enough to make her cry and affecting her activity and sleeping, was relieved by analgesic at home.

A clinical examination revealed limping, mild tenderness in the right hip, and shortening of the right limb, but no swelling, redness, or fever. Her pain score was 8 out of 10. A laboratory investigation showed hemoglobin of 8.8 g\dL (11–16 g\dL), MCV of 67.7 FI (77–93 FI), neutrophils of 12.81 10^3\UI (2–10 10^3\UI), and platelets of 325 10^3\UI (170–490 10^3\UI) (see Table 1). The radiological findings of an MRI showed bilateral femoral head signal changes with preserved AVNFH and joint space (bilateral stage 2). The patient was managed with the MTD of HU 20 mg/kg /d and followed up for two years with good improvement clinically and radiologically. In April 2017, there was an improvement in clinical manifestation, which was observed by decreased pain and limping. A laboratory investigation found hemoglobin of 10.2 g\dL (11–16 g\dL), MCV of 75.1 FI (77–93 FI), neutrophils of 10.49 10^3\UI (2–10 10^3\UI), and platelets of 494 10^3\UI (170–490 10^3\UI). Radiological examination by MRI showed an improved femoral

head after using the MTD of HU despite a new bone marrow lesion on the left side(See Figure 3).

2.3 Case 3

A Saudi girl was diagnosed with sickle cell anemia at 5 months of age, as her initial Hb electrophoresis was HbS = 84%, HbA2 = 3.3%, and HbF = 9.4%. The patient was on folic acid and low-dose HU (250 mg five days per week and 500 mg at the weekend) with good compliance. She had multiple attacks of VOC every one to two months and a history of blood transfusion. There was a positive family history of sickle cell anemia (her parents and two brothers were carriers, and one brother was affected by sickle thalassemia). She had no history of fever or major trauma.

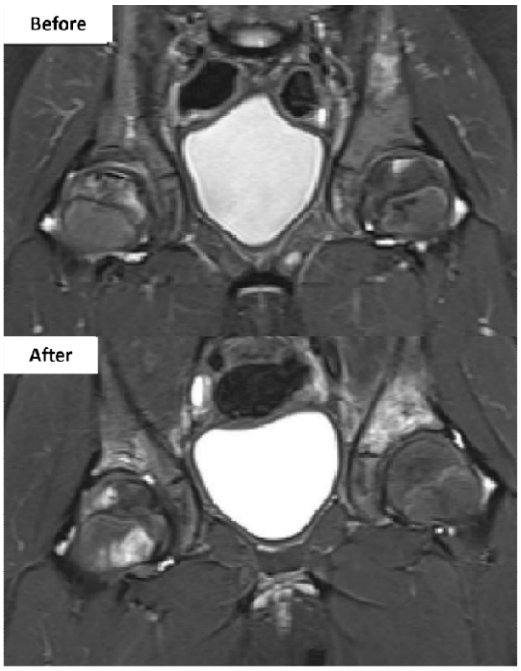


Figure 4. Case 3

In September 2015, the patient presented to the emergency room at the age of 12 years with right thigh pain that had increased gradually for six months, had not radiated, and was aggravated by walking and long standing. There were no relieving factors. A clinical examination revealed limping with shortening of the limb, but there was no tenderness, swelling, redness, or fever. Her pain score was 9 out of 10. A laboratory investigation showed hemoglobin of 8.5 g\dL (11–16 g\dL), MCV of 86 FI (77–93 FI), neutrophils of 7.5 10^3\UI (2–10 10^3\UI), and platelets of 698 10^3\UI (170–490 10^3\UI). The radiological findings of an MRI indicated bilateral femoral head signal changes with preserved AVNFH and joint space (bilateral stage 2).The patient was managed with the MTD of HU 22mg/kg/d 1,000 mg/od and followed up for four years with good clinical and radiological improvement. An improvement in clinical manifestation was observed by a decrease in pain and limping. A laboratory investigation found hemoglobin of 10.3 g\dL (11– 16 g\dL), MCV of 79.7 FI (77–93 FI), neutrophils of 3.03 10^3\UI (2–10^3\UI), and platelets of 10^3\UI (170–490 10^3\UI) (see Table 1). A radiological examination revealed that, although new bone marrow lesions had emerged, the left femoral head was restored to normal signal while the right head showed fewer signal changes (at the same stage = 2)(See Figure 4).

2.4 Case 4

A 13-year-old Saudi girl had been diagnosed with sickle cell anemia at 5 months, as her initial Hb electrophoresis was HbS = 84.4%, HbA2 = 3.9%, and HbF = 5.8%. Currently she is on folic acid 1 mg/d HU 500 mg/od, with good compliance extra prophylactic immunization. She had frequent admissions with VOC every two months and mostly with aggressive course. Of her three sisters, two exhibited sickle cell traits.

In October 2017, she presented to the emergency room with sudden onset left side hip pain for two days, stabbing in nature, not radiating, progressive, and partially relieved by analgesia, with no aggravating factors. It was associated with VOC at the time of admission. She had no history of fever or major trauma

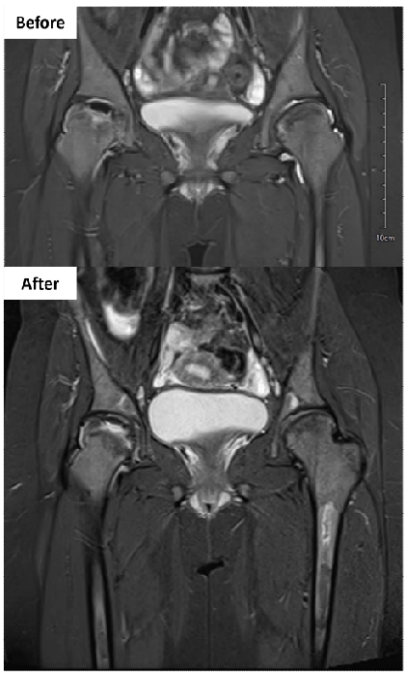


Figure 5. Case 4

A clinical examination found severe tenderness in the left leg but no limping, limitation, swelling, redness, fever, or shortening of the limb. Her pain score was 10 out of 10. A laboratory investigation showed hemoglobin of 7.9 g\dL (11–16 g\dL), MCV of 83.2 FI (77–93 FI), neutrophils of 7.90 10^3\UI (2–10 10^3\UI), and platelets of 684 10^3\UI (170–49010^3\UI).

The patient was managed with MTD of HU 20mg/kg/d 1000 mg and followed up for two years with good clinical and radiological improvement. In June 2019, an examination revealed improvement in clinical manifestations as observed by a decrease in pain and limping. A laboratory investigation showed hemoglobin of 9.97 g\dL (11–16 g\dL), MCV of 91 FI (77–93 FI), neutrophils of 8.83 10^3\UI (2–10 10^3\UI), and platelets of 374 10^3\UI (170–490 10^3\UI) (see Table 1). in 2020 she developed AVN in her other hip. Which made her a candidate for Total Hip Arthroplasty (THA)(See Figure 5).

3. Discussion

This case series demonstrates the treatment outcomes of the MTD of HU in pediatric SCD patients with AVNFH. We retrospectively identified four female patients at Maternity and Children Hospital in Makkah, KSA. The patients were treated with an MTD of HU regimen from 2015 through 2019.

Our literature review found various articles focused mainly on the treatment of AVNFH through physiotherapy or surgical intervention (core decompression or THA). Physiotherapy carries a failure risk of up to 17%, and its benefit is limited to the early stages of AVN (Mallet et al., 2018). Surgical interventions are largely effective, but core decompression is similarly limited to the early stages, and some patients need THA afterward. THA, meanwhile, is a major surgery that may be complicated by postoperative blood loss requiring transfusion and may result in transfusion reaction (or alloimmunization), acute chest syndrome, and VOC. Long- and short-term infections have also been reported (Kamath et al., 2015).

A study on isolated HU pharmacological therapy for cases of SCD with AVNFH, conducted in Kuwait City, showed its efficacy in preventing new lesions and slowing progression (Adekile et al., 2019). By contrast, another study reports that exposure to HU is a risk factor for developing AVN, but our study suggests the opposite conclusion (Kris M Mahadeo et al., 2011; Kris Michael Mahadeo et al., 2008).

The use of a highly prescribed medication for SCD, which is known to significantly reduce complications in treating the serious condition of AVN without exposing the patient to an invasive procedure, has the potential to greatly improve the quality of life of SCD patients with AVNFH. The current study used the MTD of HU as a therapy to treat pediatric sickle cell patientswith advanced AVNFH. One patient showed improvement in clinical manifestations (pain and limping) as well as in her radiological findings whereas, among the other patients, a stationary radiological course was recorded but with clinical improvement. A decreased rate of admission to the hospital due to VOC was noticeable in all patients after the HU dose was increased to the MTD. As this study report is a level-4 (weak evidence) result, further studies with large sample sizes and random controls are recommended.

(Case1)			
CBC withdi	**Pre-treatment**	**Post-treatment**	**Normalrange**

fferential			
Neutrophils%	43	32.6	40-80
Neutrophils#	2.17	1.1410	2-10
Hemoglobin	7.1	10	11-16
MCV	79.7	104	77-93
Platelet	237	261	170-490
(Case2)			
Neutrophils%	63.2%	67.8%	40-80
Neutrophils#	12.81	10.49	2-10
Hemoglobin	8.8	10.2	11-16
MCV	67.7	75.1	77-93
Platelet	325	494	170-490
(Case3)			
Neutrophils%	46.7%	29.5%	40-80
Neutrophils#	7.5	3.03	2-10
Hemoglobin	8.5	10.3	11-16

MCV	86	97.7	77-93
Platelet	698	432	170-490
(Case4)			
Neutrophils%	53.8%	52.2	40-80
Neutrophils#	7.90	8.83	2-10
Hemoglobin	7.9	9.97	11-16
MCV	83.2	91	77-93
Platelet	684	374	170-490

Table1. Laboratory investigations of the reported patients(n=4).

Casenumber	Genotype	Status
1	SS	Stable
2	SS	Improved
3	SS	Stable
4	SS	Stable

Table 2. Genotypes of the reported patients (n = 4).

4. Conclusion

Our study found clinically and radiologically significant improvement in patients who were prescribed the MTD of HU. However, this report is level 4 (weak evidence), so we recommend further studies with larger sample sizes and randomization.

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