Abstract

Hydroxyurea is a key treatment option for patients having sickle cell disease. Although the treatment has been effective in improving the survival rate, new concerns over improving quality of life are forthcoming due to spermatogenesis-related toxicities and teratogenic effects. The available evidence shows that hydroxyurea might exacerbate the existing sperm abnormalities. There is a lack of comprehensive, systemic evidence to demonstrate the precise effects and role of hydroxyurea on sperm abnormalities in patients with sickle cell disease. Patients and healthcare providers require accurate and extensive information on sperm-related toxicities to make informed decisions. Here, I discuss the effects of hydroxyurea (HU) on sperm parameters, clinical study evidence, and treatment options available for fertility preservation in these patients.

Keywords: Sickle cell disease, Hydroxyurea, Sperm abnormalities.

Introduction

Sickle cell disease (SCD) is a group of genetic blood disorders that leads to abnormality in hemoglobin. In patients with SCD, newer medical treatments have improved survival rates and quality of life along with a reduced disease-related morbidity. Consequently, the focus of the treatment is diverging to encompass the reproductive issues associated with these treatments.

In adolescents and young patients with SCD, sexual maturation is delayed by 1.5-2 years [1, 2], and approximately 24% of SCD patients may have hypogonadism, infertility, erectile dysfunction, and poor libido [3]. The issues related to fertility and reproductive organs in SCD are either related to disease or to the treatments used to treat SCD-related morbidity.

Reduced SCD-related morbidity has been observed with treatments like hydroxyurea (HU) and hematopoietic stem cell transplantation (HSCT). However, adverse effects and toxicities associated with these therapies are a concern. HU use has been associated with sperm abnormalities and teratogenic effects [4, 5]. However, HU affects rapidly dividing cells, raising concerns about related toxicities. Therefore, it is essential to evaluate if there is an exacerbation of fertility problems in men with SCD. This review summarizes the spermatogenic effects of HU in males with SCD.

Fertility issues in males with SCD

Some of the disease-related fertility issues observed in patients with SCD are hypogonadism, sperm abnormalities, erectile dysfunction, delay in sexual maturation, and abnormal hormone (testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH)) levels.

The sperm abnormality rate is as high as 91% in males with SCD [6]. Although some reports attribute sperm abnormalities to delayed puberty in males with SCD [7], some others attribute it to testicular infarction or hypogonadism. It is
also worth noting that sperm abnormalities also exist with normal testosterone, FSH, and LH levels [8].

In addition to sperm abnormalities, the incidence of erectile dysfunction in men with SCD is reported to be 21%–35% [9-11]. Also, a decrease in semen is reported in men with SCD [12]. Laboratory findings show low testosterone levels with variable FSH and LH levels. Moreover, abnormalities in accessory organs like seminal vesicles and prostate glands may be present due to recurrent urinary tract infections. These reproductive issues are exacerbated by therapies like HU, which have therapeutic effects through impairing DNA synthesis.

**HU in treatment of SCD**

HU is approved for the prevention of vaso-occlusive pain in SCD. HU is a ribonucleotide reductase inhibitor that impairs DNA synthesis due to its S-phase-specific cytotoxic action. It is an antimitotic agent that can impair human spermatogenesis.

It is a disease-modifying therapy that decreases episodes of acute pain and acute chest syndrome in SCD patients [13]. The HU therapy increases the fetal haemoglobin, which does not sickle under low oxygen tension. Low-dose HU therapy (10 mg/kg/day) has been effective in improving clinical and hematological parameters, reducing painful crises, and reducing blood transfusion requirements in SCD patients. Although HU has improved the quality of life and survival rate, its use is limited by its toxicities, particularly its effect on fertility parameters.

SCD itself manifests in some abnormalities like spermatogenesis, and seminal fluid, which may be exacerbated with cytotoxic HU therapy. HU is associated with abnormal sperm morphology [14] and a decrease in sperm count [14-16] in patients with SCD. At a therapeutic dose, it has short-lived, irregular cytotoxic effects on dividing cells [4]. Since it is an antimetabolite, it is hypothesized to have a risk of affecting sperm development [4]. These effects are often brief and reversible with discontinuation of the drug administration.

**Infertility in Men with SCD**

Although HU treatment has improved outcomes in patients with SCD, it has been associated with effects on spermatogenesis and teratogenicity, for example, testicular atrophy, hypogonadism, decreased sperm count, abnormal sperm motility, and abnormal sperm morphology.

**Hypogonadism**

Male hypogonadism is decreased functional activity of the gonads that results in a testosterone deficiency. Testosterone deficiency can cause infertility, muscle wasting, and the absence of secondary sex characteristics. The mechanism for the cause of hypogonadism may be primary gonadal failure [17-19], repeated testicular infarction [20], zinc deficiency [21, 22], and partial hypothalamic hypogonadism [23].

**Abnormal spermatogenesis**

Impaired spermatogenesis has been reported in male patients with SCD receiving HU therapy, which leads to testicular atrophy, oligozoospermia (low sperm count), abnormal sperm morphology, and azoospermia (decreased sperm motility) [6, 15, 16, 24-31]. It is yet unclear if the abnormalities directly affect HU therapy. However, some researchers believe that the extent of sperm abnormalities might be associated with the length of HU therapy [29, 30]. Since SCD is a genetic condition manifesting at an early age, the duration of HU therapy remains long.

**Abnormal Hormone level**

A few studies have reported altered levels of testosterone and dihydrotestosterone, FSH, and LH in patients with SCD [12, 32, 33]. The testosterone levels have a direct effect on fertility [6], reduction in semen volume, sperm count, and motility in sickle cell male patients [10].

**Priapism**

Priapism is defined as a prolonged and lasting continued penile erection unrelated to sexual interest or stimulation [34]. The prevalence of priapism and erectile dysfunction in patients with SCD is 45% and 30%, respectively [35-37].

Penile erection is regulated by the neurotransmitter nitric oxide (NO). In SCD patients, the bioavailability of NO is decreased, disturbing the relaxation of penile smooth muscle [38, 39]. Also, the adenosine regulation pathway might be contributing to the pathophysiology of priapism in SCD patients.

**Studies evaluating the effect of HU therapy on spermatogenesis SCD patients**

Several studies have reported the role of HU in the exacerbation of various sperm abnormalities in patients with SCD.

A non-interventional study (ESCORT-HU-European Sickle Cell Disease Cohort-Hydroxyurea) evaluated safety, morbidity, and mortality in 422 SCD patients of age 15 years and older treated with HU [40, 41]. The study reported 67 pre-treatment and 24 during treatment semen analyses. Before treatment with HU, 49% of sperm analyses were normal, and 25% were abnormal (at least 1 abnormality: sperm mobility, sperm count, appearance).
The rate of abnormalities during HU treatment increased to 50%. The abnormalities observed were asthenospermia, hypospermia, oligospermia, azoospermia, and atypical forms. These results confirmed that sperm abnormalities are exacerbated after HU treatment.

A prospective, Phase 4 multicentre study called HYDREP (NCT01609192) assessed the effect of HU treatment in patients with SCD [42]. The study reported a significant and rapid decrease in mean total sperm count from 129.8 million at baseline to 24.1 million at month 6. Furthermore, 86% of patients had an abnormal value of total sperm count at month 6 compared to only 40% at baseline. Researchers also found that 6 months of HU treatment did not affect the semen volume. They reported that the treatment of SCD with HU causes significant abnormality in spermatogenesis. After treatment, the number of men with abnormal total sperm count and cryptozoospermia increased to 30 patients and 5 patients, respectively. Additionally, six patients (17%) became azoospermic, and 19 were oligozoospermic.

An unmatched case-control study in Nigeria compared serum testosterone concentration among 47 patients with hemoglobin phenotype SS and 28 volunteers with hemoglobin phenotype AA [43]. The concentrations of serum testosterone in 44 of 47 hemoglobin phenotype SS patients were significantly lower as compared to 7 of 28 volunteers with hemoglobin phenotype AA.

A group of researchers evaluated the effect of long-term HU treatment from childhood to adult age in four patients [44]. These patients were receiving HU treatment for more than 8 years. They observed that two patients experienced severe oligozoospermia and two azoospermia. The treatment exposure in patients experiencing oligozoospermia was shorter (8 and 9 years) compared to patients experiencing azoospermia (12 and 15 years). There was also an increased percentage of abnormal spermatozoa morphology in these patients.

Furthermore, a study assessed spermatogonial quantity in prepubertal patients who received alkylating agents to compare with patients who received non-alkylating agents. They demonstrated that the quantity of spermatogonia per transverse tubular cross-section was significantly low in patients with SCD receiving hydroxyurea (0.3 ± 0.6, n = 6; P = 0.008) [45]. Contrarily, a recent study reported no difference in semen volume, sperm concentration, total sperm count, or spermatozoa motility, morphology, and vitality between patients with SCD who received HU before puberty and who did not receive HU during puberty [46].

**Semen analysis**

A significant reduction in sperm density, ejaculate volume, sperm motility was reported in the SCD patients compared to the control subjects [43]. Likewise, some former studies that performed semen analysis in men with SCA reported a reduction in sperm motility, sperm density, and sperm morphology [44]. Similarly, Osegbe et al. and Agbaraji et al. analyzed sperm density, motility, morphology, and semen volume in patients with SCD. They reported a decrease in sperm motility, sperm density, and abnormal morphology in patients with SCD. [12, 47] Osegbe et al. observed no difference in semen volume [33]. Additionally, Friedman et al. reported oligospermia in 3 out of 4 patients with SCD [47].

Similar to Osegbe et al., a recent study also reported a normal volume of ejaculate in 75% of the samples of SCD patients. However, all sperm parameters during HU treatment were affected [47]. There were no incidents of azoospermia in five patients, although a marked decrease in sperm density during the HU treatment compared to before the HU treatment was reported. Interrupting HU treatment did not help recuperate the sperm parameters to initial levels.

However, before HU was established as a standard of care to treat SCD, subfertile range sperm parameters had been reported in patients. More recent studies have reported at least one abnormal sperm parameter in about 90% of patients [47].

HU treatment, even in low doses, exacerbates sperm parameters abnormalities in SCD patients. Therefore, routine seminal fluid parameters assessment is recommended to monitor sperm parameter changes during treatment with HU.

**Treatments Available**

For patients who have abnormal spermatogenesis due to their underlying condition or treatment of the conditions, the option of fertility preservation can be considered. The “optimal” age for fertility preservation is still a discussion. Below are some of the options available [46]-

- Erectile dysfunction can be managed with penile implants effectively
- Testicular tissue cryopreservation
- Gonadal shielding
- Sperm cryopreservation
- Testicular sperm extraction
• Electroejaculation—electrical current to trigger ejaculation.

• Symptoms of hypogonadism can be treated with testosterone undecanoate injections\textsuperscript{12} and clomiphene\textsuperscript{13}

In prepubertal males, patients have very limited experimental options, for example, removal and preservation of part of the testicle [47]. However, there have been no reports of live human births from re-implanted testicular tissue yet.

Counseling about infertility risk associated with the disease and treatments, and options for fertility preservation is important in these situations. Many unresolved ethical dilemmas arise for pediatric patients regarding counseling about fertility issues and preservation. The first dilemma is with whom the responsibility of making the decision should rest. Although some guidelines consider it should be parents, often patients (mostly children in case of SCD) and parents may have different opinions and choices. The American Academy of Pediatrics has published guidelines encouraging healthcare providers to discuss the issues and options with patients and guardians [48].

Since fertility preservation may not be feasible in all cases of SCD, regular monitoring for sperm abnormalities during HU therapy has been suggested.

Conclusions

HU has significantly improved the treatment outcomes in SCD patients. However, some concerns regarding the cytotoxic effects of HU on spermatogenesis emerge. Extensive research is required to evaluate the before and after treatment sperm parameters and the effects of treatment with HU on spermatogenesis.

Newer medical advances have improved survival rates and reduced disease-related morbidity in SCD patients, bringing reproductive issues to the forefront. Prospective, large population-based studies among patients with SCD are required to determine cellular and functional impairment of fertility and evaluate the impact of HU therapy on the impairment.

The clinical practice and future research should be streamlined to focus on improving the quality of life along with the prognosis of the patients. The patient-centric research will help in better management and treatment of patients with SCD with HU therapy.

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