Effect of Hydroxyurea on Sperm Parameters in Sickle Cell Anemia and Thalassemia Intermedia

Thesis

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Ghada Mamdouh Mohamed Fawzy

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List of Abbreviations

Abbr.	Title
ATF2	: Activation of transcription factor
BT	: Beta-thalassemia
BTI	: Beta thalassemia intermedia
DFO	: Deferoxamine
DFP	: Deferiprone
DFX	: Deferasirox
DVT	: Deep vein thrombosis
EMH	: Extramedullary hematopoiesis
FSH	: Follicle-stimulating hormone
GDF15	: Growth and differentiation factor 15
GnRH	: Gonadotrophin-releasing hormone
GWAS	: Genome wide association studies
Hb	: Hemoglobin
HbF	: Fetal hemoglobin
HIC	: Hepatic iron content
HIFs	: Hypoxia-inducible transcription factors
HLA	: Human leukocyte antigen
HU	: Hydroxyurea
LH	: Luteinizing hormone
MCH	: Mean corpuscular Hb
MCV	: mean corpuscular volume

MRI : Magnetic resonance imaging

MUGA : Multiple gated acquisition scan

NO : Nitric oxide

PHT : Pulmonary hypertension

RE : Reticuloendothelial

ROS : Reactive oxygen species

SCA : Sickle cell anemia

SCFAD : Short chain fatty acid derivative

SD : Standard deviation

SPSS : Statistical Package for Social Science

TI : Thalassemia intermediate

TM : Thalassemia major

TSC : Total sperm count

UDPG : Uridine 5'diphospho-alpha-D-glucose

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Abstract

Background: Thalassemias are genetic disorders in globin chain production. In individuals with Beta -thalassemia, there is either a complete absence of β-globin gene production (β0 -thalassemia) or a partial reduction (β+-thalassemia). **Aim of the Work:** Assessment of the effect of hydroxyurea treatment in patients with thalassemia intermedia on sperm parameters. This is accomplished by assessment of sperm parmeters at base line and reassessment after six month of treatment. **Patients and Methods:** This was a prospective follow-up study that included 10 fully pubertal patients with thalassemia intermedia who presented to the Haematology/Oncology Clinic at the Pediatrics Hospital, Ain Shams University. Verbal consents were obtained from the patients before enrollment in the study. The study protocol was approved by our localethical committee. **Resuts:** This study revealed that there were statistically a high difference between patients receiving hydroxyurea and those not receiving hydroxyurea in the first lab regarding Total sperm count ($p<0.001$). There were statistically a high significant difference between base line semen analysis and follow up semen analysis in patients receiving hydroxyurea regarding Total sperm count ($p < 0.001$).There was statistically a high significant difference between total sperm count total sperm count in million patients on hydroxyurea treatment 6.33 ± 3.54 (1-10.2) and patients six month off hydroxyurea treatment 45.99 ± 28.03(8.5-88) in patients receiving hydroxyurea ($t= -5.252$, $p < 0.001$).There were statistically high significant relations of total sperm count in patients on hydroxyurea treatment with hydroxyurea dose, hydroxyurea complinance and duration in patients receiving hydroxyurea ($p < 0.05$). There were statistically significant relations of total sperm count in patients six month off hydroxyurea treatment with hydroxyurea dose, hydroxyurea compliance and duration in patients receiving hydroxyurea ($p < 0.05$). **Conclusion:** HU is a safe medication in thalassemic patients, saving in blood transfusion costs and disease complications is remarkable.

Key words: Thalassemia intermedia, hydroxurea, sperm parameters, sickle cell anemia

Introduction

Thalassemia intermedia (TI) has a wide clinical spectrum extending between the clinically severe thalassemia major (TM) on the one end and the asymptomatic thalassemia carrier state on the other end**.** It accounts for up to 25% of cases of β-thalassemia patients**.** It occurs with equal frequency in males and females **(Yaish, 2011).**

Spermatogenesis is a dynamic, continuous process in which diploid spermatogonia undergo ten mitotic and two meiotic divisions to differentiate into haploid spermatozoa. The production of sperm is dependent on the presence of spermatogonial stem cells that reside in the basal compartment of the seminiferous tubules, and which represent a very small proportion of the cells in the testis. Spermatogenesis involves 4 sequential processes: spermatogonial proliferation and differentiation, meiosis of spermatocytes, spermiogenesis and spermiation **(Amann, 2008)**.

Hydroxycarbamide or hydroxyurea is an anti-neoplastic drug, first synthesized in 1869, used in myeloproliferative disorders, specifically polycythemia vera and essential thrombocythemia. It is also used to reduce the rate of painful attacks in sickle-cell disease and has antiretroviral properties in diseases such as HIV/AIDS. It is on the World Health Organization's List of Essential Medicines, a list of the most

important medication needed in a basic health system. Hydroxyurea has been reported as endogenous in human blood plasma at concentrations of approximately 30 to 200 ng/mL **(Rustin, 2012)**.

Kosaryan et al. (2009) concluded that HU is a safe medication in thalassemic patients. Saving in blood transfusion costs and disease complications is remarkable. Relatively mild and transient side effects are tolerable, yet patients are to be supervised periodically and when they are anemic there must be immediate access to the hospital.

Aim of the Work

Assessment of the effect of hydroxyurea treatment on sperm parameters by semen analysis before and six months after treatment.

Thalassemia Intermedia

Thalassemia intermedia (TI) has a wide clinical spectrum extending between the clinically severe thalassemia major (TM) on the one end and the asymptomatic thalassemia carrier state on the other end **(Taher et al., 2006).** Thalassemia intermedia (TI) was first illustrated in 1955 by Rietti–Greppi–Micheli, who described patients as being 'too hematologically severe to be called minor, but too mild to be called major.

Incidence:

Thalassemia intermedia accounts for up to 25% of cases of β-thalassemia patients**.** It occurs with equal frequency in males and females **(Yaish, 2011).**

Age of Presentation:

Thalassemia intermedia usually presents between the ages of 2 and 6 years. Mildly affected patients are completely asymptomatic until adult life, experiencing only mild anemia and maintaining hemoglobin levels between 7 and 10 g/dl, and their diagnosis is made by chance **(Yaish, 2005 and Taher et al., 2006).**

Genotype/Phenotype correlation in Thalassemia Intermedia:

Nevertheless, because of several factors that interact in the disease expression, the β-genotype alone is not predictive