

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

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبناك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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List of Contents

<i>Subject</i>	<i>Page No.</i>
List of Abbreviations.....	i
List of Tables.....	iii
List of Figures	iv
Introduction	1
Aim of the Work.....	3
Review of Literature	4
Patients and methods	43
Results.....	48
Discussion	64
Summary	72
Conclusion and Recommendations.....	75
References	76
Arabic Summary	—

List of Abbreviations

<i>Abbr.</i>	<i>Title</i>
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

List of Tables

<i>Table No.</i>	<i>Title</i>	<i>Page No.</i>
Table (1):	Lower reference limits for semen characteristics	46
Table (2):	Clinico epidemiological characteristics of the studied patients	48
Table (3):	Comparison between patients receiving hydroxyurea and those not receiving hydroxyurea regarding clinical demographic characteristics	50
Table (4):	Comparison between patients receiving hydroxyurea and those not receiving hydroxyurea regarding first lab	51
Table (5):	Comparison between patients receiving hydroxyurea and those not receiving hydroxyurea regarding follow up semen analysis	53
Table (6):	Comparison between base line semen analysis and follow up semen analysis in patients not receiving hydroxyurea	54
Table (7):	Comparison between base line semen analysis and follow up semen analysis in patients receiving hydroxyurea	55
Table (8):	Comparison between total sperm count in million in patients on hydroxyurea treatment and patients six month off hydroxyurea treatment in patients receiving hydroxyurea	57
Table (9):	Relation of total sperm count in patients on hydroxyurea treatment with hydroxyurea dose, compliance of hydroxyurea and duration in patients receiving hydroxyurea	58
Table (10):	Relation of total sperm count in million in patients six month off hydroxyurea treatment with hydroxyurea dose, hydroxyurea compliance and duration in patients receiving hydroxyurea	61

Table (11): Relation of total sperm count in patients on hydroxyurea treatment and in patients six month off hydroxyurea treatment with hemoglobin and serum ferritin levels in patients receiving hydroxyurea	63
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List of Figures

<i>Figure No.</i>	<i>Title</i>	<i>Page No.</i>
Figure (1):	Spermatogenesis: Within the seminiferous tubules (Samplaski et al. 2010).....	27
Figure (2):	Hormone circuitry of hypothalamo-pituitary-testicular axis. Ant. indicates anterior; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone (Madhukar and Rajender, 2009).....	28
Figure (3):	Schematic representation of potential antagonistic mechanisms affecting cellular and hemoglobinization responses of R- and NR-cells. Bold arrows: strong effects; dashed arrows: weak effects.	39
Figure (4):	Transfusion history of the studied patients	48
Figure (5):	Hydroxyurea therapy of studied patients	49
Figure (6):	Compliance of studied patients to Hydroxyurea therapy	49
Figure (7):	Comparison between patients receiving hydroxyurea and those not receiving hydroxyurea in base line semen analysis regarding total sperm count.....	52
Figure (8):	Comparison between base line semen analysis and follow up semen analysis in patients not receiving hydroxyurea regarding total sperm count.....	54
Figure (9):	Comparison between base line semen analysis and follow up semen analysis in patients receiving hydroxyurea regarding total sperm count.....	56
Figure (10):	Comparison between total sperm count in million in patients on hydroxyurea treatment and patients six month off hydroxyurea treatment in patients receiving hydroxyurea.....	57

List of Figures

Figure (11): Relation of total sperm count in million in patients on hydroxyurea treatment with hydroxyurea dose in patients receiving hydroxyurea	59
Figure (12): Relation of total sperm count in million in patients on hydroxyurea treatment with duration in patients receiving hydroxyurea.....	60
Figure (13): Relation of total sperm count in million in patients six month off hydroxyurea treatment with hydroxyurea dose in patients receiving hydroxyurea.....	62
Figure (14): Relation of total sperm count in million in patients six month off hydroxyurea treatment hydroxyurea compliance with in patients receiving hydroxyurea.....	62
Figure (15): Relation of total sperm count in million in patients six month off hydroxyurea treatment with duration in patients receiving hydroxyurea	63

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 (β^0 -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 parameters 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. **Results:** 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 complinace 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

*A*ssessment 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