

**Rigiscan and Patient Monitored
Comparative Efficacy of Continuous Use of
Short and Long acting Phosphodiesterase
Inhibitors in Arteriogenic Erectile
Dysfunction**

Thesis

*Submitted for Partial Fulfillment of Master Degree
in Dermatology, Venereology and Andrology*

Presented By

Ahmed Mohsen Ahmed Amin
(M.B., B.Ch)

Supervised by

Prof. Dr. Adel Ahmed Halim Emam
Chairman and Professor of Dermatology, Venereology and
Andrology
Faculty of Medicine - Ain Shams University

Prof. Dr. Samar Abdallah Mohamed Salem
Professor of Dermatology, Venereology and Andrology
Faculty of Medicine - Ain Shams University

Dr. Daa Eldine Darwish Ali Gamil
Chairman and Consultant of
Dermatology, Venereology and Andrology
Elmatariya Teaching Hospital

Faculty of Medicine
Ain Shams University
2011

المقارنة بين أثر الاستخدام المستمر لمتبذات الفوسفوديستراز
قصيرة وطويلة المفعول في ضعف الانتصاب الشرياني عن طريق
رصد المريض و جهاز الريحيسكان

رسالة

توطئة للحصول على درجة الماجستير في الأمراض الجلدية والتناسلية
وأمرض الذكورة

مقدمة من الطبيب

أحمد محسن أحمد أمين

بكالوريوس الطب والجراحة

تحت إشراف

أ.د/ عادل أحمد حليم إمام

أستاذ ورئيس قسم الأمراض الجلدية والتناسلية وأمراض الذكورة
كلية الطب جامعة عين شمس

أ.د / سمر عبد الله محمد سالم

أستاذ الأمراض الجلدية والتناسلية وأمراض الذكورة
كلية الطب جامعة عين شمس

د / ضياء الدين درويش علي جميل

استشاري ورئيس قسم الأمراض الجلدية والتناسلية وأمراض الذكورة
مستشفى المطرية التعليمي

كلية الطب
جامعة عين شمس
٢٠١١

Summary

Erectile dysfunction is defined as the consistent or recurrent inability to attain and/or maintain an erection sufficient for a satisfactory sexual intercourse.

Erectile dysfunction does not only affect men's sex life, but also significantly affects their overall satisfaction with life in general and it has a notable impact on the quality of life of patients and their partners.

Erectile dysfunction is correlated with age; in Egypt it has 26% prevalence at the age of 50 years, 49% prevalence at the age of 60 years and 52% prevalence at the age of 70 years or older. ED can be classified as psychogenic, organic (vascular, diabetic, drug-induced, traumatic, neurogenic and hormonal) or mixed psychogenic and organic.

The International Index of Erectile Function (IIEF) has been shown to be a cross-culturally and psychometrically valid measure of male erectile dysfunction.

Rigiscan device is one of the most reliable tests commonly used to monitor penile rigidity and tumescence. It consists of two loops, one placed around the base of the penis and the other at the tip of the penis, proximal to the coronal sulcus, as well as a recording unit that is strapped to the patient's thigh.

Trials in which PDE5 inhibitors were used to treat ED have mostly involved use of the drug in an on-demand schedule

O

وَقَالُوا بَدَّأَكَ لَا عِلْمَ لَنَا
بِمَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ
الْحَكِيمُ

صدق الله العظيم

سورة البقرة الآية

(٢٦)

Acknowledgment



First of all, thanks to **Allah** the most merciful for giving me the strength to complete this work.

I wish to express my deepest thanks and respect to **Prof. Dr. Adel Ahmed Halim Emam**, Chairman and Professor of Dermatology, Venereology and Andrology,, Faculty of Medicine, Ain Shams University, for his valuable supervision, guidance and kind advice throughout this work.

Special thanks and deepest gratitude to **Prof. Dr. Samar Abdallah Mohamed Salem**, Professor of Dermatology, Venereology and Andrology, Faculty of Medicine, Ain Shams University, for her good support, continuous supervision and unlimited help during this work.

I would like to express my gratitude and appreciation to **Dr. Diaa Elidine Darwish**, Consultant and Chairman of Dermatology, Venereology and Andrology, Elmatariya Teaching Hospital, for his sincere scientific and moral help.

Ahmed Mohsen

List of Contents

Title	Page
• List of Abbreviations	II
• List of Tables	V
• List of Figures	VIII
• Introduction and Aim of the Work	1
• Review of Literature:	
▪ Chapter 1: Anatomy and Physiology of Erectile Dysfunction	4
* 1.1. Anatomy of Penis	4
* 1.2. Physiology of Penile Erection	8
▪ Chapter 2: Erectile Dysfunction	16
* 2.1 Definition of Erectile Dysfunction	16
* 2.2 Incidence of Erectile Dysfunction	17
* 2.3 Classification of Erectile Dysfunction	17
* 2.4 Pathophysiology of Erectile Dysfunction	19
* 2.5 Diagnosis of Erectile Dysfunction	28
* 2.6 Treatment of Erectile Dysfunction	45
▪ Chapter 3: Phosphodiesterase Inhibitors	61
* 3.1 Classification of Phosphodiesterase Inhibitors	61
* 3.2 Phosphodiesterase 5 Inhibitors	62
• Patients and Methods	82
• Results	98
• Discussion	125
• Summary	136
• Conclusion and Recommendations	141
• References	142
• Appendix	166
• Arabic Summary	--

List of Abbreviations

>	More than
<	Less than
≥	More than or equal
%	Percent
α	Alpha
β	Beta
μg	Micro gram
ACEIs	Angiotensin converting enzyme inhibitors
B-mode	Brightness modulation
BPH	Benign prostatic hyperplasia
BSM	Bulbospongiosus muscle
Ca ²⁺	Calcium ion
cAMP	Cyclic adenosine mono-phosphate
CBC	Complete blood count
CC	Corpora cavernosa
CCB	Calcium channel blockers
cGMP	Cyclic guanosine mono-phosphate
C _{max}	Maximum plasma concentration
CNS	Central nervous system
CS	Corpus spongiosum
D ₁ /D ₂	Dopaminergic receptors
DICC	Dynamic infusion pharmacocavernosometry and cavernosography
DM	Diabetes mellitus
ED	Erectile Dysfunction
EDV	End diastolic velocity

EF	Erectile function
e.g	For example
EHNA	Erythro-9-2-hydroxy-3-nonyl adenine
FDA	Food and Drug Administration
Fig	Figure
H	Hour
H2	Histamine receptor type 2
Hg	Mercury
HS	Highly significant
HTN	Hypertension
IBMX	3-isobutyl-1-methylxanthine
ICI	Intracavernosal injection
ICM	Ischiocavernosus muscle
ICP	Intracavernosal pressure
IIEF	International Index of Erectile Function
K ⁺	Potassium ion
LH	Luteinizing hormone
LUTS	Lower urinary tract symptoms
MAOI	Monoamine oxidase inhibitors
Mg	Milligram
MHZ	Mega Hertz
ml	Milliliter
mm	Millimeter
MRI	Magnetic resonance imaging
MUSE	Medicated urethral system for erection
NO	Nitric oxide
NPT	Nocturnal penile tumescence

NS	Non significant
PBI	Penile brachial index
PDEs	Phosphodiesterases
PE	Premature ejaculation
PET	Positron emission tomography
PG	Prostaglandin
PPUD	Pharmaco penile duplex ultrasound
P/R	Per rectum
PSV	Peak systolic velocity
r	Pearson correlation coefficient
RAU	Rigidity activity unit
REM	Rapid eye movement
RI	Resistive index
S	Significant
Sec	Second (unit of time)
SIEDY	Structured Interview on Erectile Dysfunction
Sis	Structured interviews
SLx-2101	Surface Logix-2101
SRQs	Self-reported questionnaires
SSRI	Selective serotonin reuptake inhibitors
TAU	Tumescence activity unit
T _{1/2}	Time required for elimination of one-half of drug
T _{max}	Time required for attaining maximum plasma concentration
Tum	Tumescence
USA	United States of America

List of Tables

<i>Table</i>	<i>Title</i>	<i>Page</i>
1	Drugs causing erectile dysfunction.	24
2	Features differentiating psychogenic from organic erectile dysfunction.	30
3	Summary of the laboratory tests in erectile dysfunction and the indications for them.	33
4	Available alternative drugs with lower risk of erectile dysfunction.	48
5	Common intracavernous agents.	55
6	Pharmacokinetic Parameters of the Phosphodiesterase 5 Inhibitors.	72
7	Common adverse events of the three phosphodiesterase 5 inhibitors used to treat erectile dysfunction.	73
8	Rigiscan Plus Summary Analysis Statistics.	88
9	Scoring system of the questionnaire.	93
10	Comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard age, occupation, and history of smoking, DM, hypertension or drug intake.	99
11	Comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard IIEF EF domain scores.	100
12	Changes in IIEF EF domain scores among group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) from baseline till 2 months.	102

<i>Table</i>	<i>Title</i>	<i>Page</i>
13	Comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard erectile event duration of real time monitoring rigiscan results.	103
14	Changes in erectile event duration of real time monitoring rigiscan results among group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) from baseline till 2 months.	105
15	Comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard tip and base rigidity.	106
16	Changes in tip and base rigidity among group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) from baseline till 2 months.	109
17	Comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard tip and base event tumescence % >base line %.	111
18	Changes in tip and base event tumescence % >base line % among group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) from baseline till 2 months.	113
19	Comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard tip and base Rau.	115
20	Changes in tip and base Rau among group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) from baseline till 2 months.	117

<i>Table</i>	<i>Title</i>	<i>Page</i>
21	Comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard tip and base Tau.	119
22	Changes in tip and base Tau among group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) from baseline till 2 months.	121
23	Correlation between IIEF EF domain and rigiscan results after treatment regimen among group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group).	122
24	Appendix I : group A.	166
25	Appendix II : group B.	167
26	Appendix III : group C.	168

List of Figures

<i>Fig</i>	<i>Title</i>	<i>Page</i>
1	Penile anatomy.	4
2	Diagrammatic representation of penile arterial system.	6
3	Venous drainage of the penis.	6
4	Innervation of the penis.	7
5	Penile erection occurs in response to various stimuli. These stimuli are integrated supra-spinally and spinally and reach the penile erectile tissues and start the erection.	8
6	Diagrammatic representation of sinusoidal filling and venous occlusion mechanism. The left diagram represents the flaccid penis and the right the erect penis.	10
7	Molecular mechanism of penile smooth muscle contraction.	14
8	Molecular Mechanism of Penile smooth muscle relaxation.	15
9	Pathophysiology of erectile dysfunction in vascular diseases.	21
10	Algorithm for the diagnostic approach of patients with erectile dysfunction.	28
11	Rigiscan device.	35
12	NPT recording in a patient with psychogenic erectile dysfunction. Five well-defined events are recorded with more than 10 minutes duration and rigidity at tip of penis more than 70%. This is a classic normal recording.	38
13	NPT recording in a patient with mixed vasculogenic erectile dysfunction. Three erectile events are recorded but not meet the definition of normal events. This is classic abnormal recording in	39

<i>Fig</i>	<i>Title</i>	<i>Page</i>
	vasculogenic cases.	
14	NPT recording in a patient with mixed vasculogenic erectile dysfunction. Four erectile events are recorded but only one meets the “best erection” normal criteria. No definite diagnosis can be made from this recording and this man could be erroneously defined as psychogenic erectile dysfunction (mixed vasculogenic cause of erectile dysfunction proved by dynamic infusion cavernosometry and cavernosography.	39
15	Normal cavernosal artery. Duplex sonogram with Doppler gate placed over cavernosal artery (top) and spectral waveform (bottom) caliper indicate PSV is 38cm/sec.	43
16	Usage of Medicated Urethral System for Erection (MUSE).	51
17	Vacuum device. (a) a plastic cylinder, which covers the penis; (b) a pump, which draws air out of the cylinder; and (c) an elastic constricting ring.	53
18	Intracavernosal injection.	57
19	Demonstration of inflatable penile prostheses in place.	58
20	Schematic diagram illustrating the mechanism of action of the phosphodiesterase 5 inhibitors.	68
21	Structures of the phosphodiesterase 5 inhibitors.	69
22	Patient during real time monitoring rigiscan test.	87
23	Data Output From a Real-time, Provocative RigiScan Monitoring Session. Rigidity and tumescence for penile tip and base are presented. Each vertical bar represents a rigidity measurement (% of a steel bar) taken every 30 seconds. Screen width = 1 hour.	87
24	Graphical comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard IIEF EF domain scores.	100

<i>Fig</i>	<i>Title</i>	<i>Page</i>
25	Graphical comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard erectile event duration of real time monitoring rigiscan results.	103
26	Graphical Comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard tip and base rigidity.	107
27	Graphical comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard tip and base event tumescence % >base line %.	111
28	Graphical Comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard tip and base Rau.	115
29	Graphical Comparison between group A (firstly sildenafil treated group), group B (firstly tadalafil treated group) and group C (placebo treated group) as regard tip and base Tau.	119
30	Scatter diagrams showing correlation between IIEF EF domain scores and rigidity (A), event tumescence (B), RAU (C) and TAU (D) after treatment regimen among group A (firstly sildenafil treated group). There is a positive linear relationship.	123
31	Scatter diagram showing correlation between IIEF EF domain scores and rigidity after treatment regimen among group B (firstly tadalafil treated group). There is a positive linear relationship.	124
32	Scatter diagram showing correlation between IIEF EF domain scores and rigidity after treatment regimen among group C (placebo treated group). There is a positive linear relationship.	124