Comparative study between Dapoxetine Hydrochloride and Tramadol Hydrochloride in Treatment of Primary Premature Ejaculation as on demand therapy

Thesis
Submitted for Partial Fulfillment of Master Degree (M.Sc)
in
UROLOGY

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Abstract

PE is recognized to be the most common male sexual disorder. It affects 30-40% of sexually active men. It is now classified into 4 types; primary (lifelong), secondary (acquired), natural variable and Premature-like ejaculatory dysfunction.

Primary PE is now finally defined by the ISSM as; ejaculation which always or nearly always occurs within or less than one minute of IELT, in all or nearly all sexual acts and cause negative personal consequences for one or both partners.

In this study we compared the effect of on demand use of Dapoxetine 30mg with Tramadol hcl 50mg with placebo

Keywords:

Prinay pru mutm E Juch

Dapoxetine , Tramadol of ISSM

Lifelong , Acguired ,AIPE .

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LIST OF ABBREVIATIOS

5-HIAA	*5-HYDROXYINDOLEACETIC ACID*
5-HT	*5-hydroxy tryptamin*
5-HTT	*5-hydroxy tryptamin transporters*
AEs	*Adverse events*
AIPE	*Arabic Index of Premature Ejaculation*
APA	*American Psychiatric Association*
AUC	*Area under the curve*
B-AR	*B-AdrenergicReceptor*
BNSTpm	*Posteromedial part of the Bed nucleus of the stria terminalis*
CNS	*Central nervous system*
Cmax	*Peak plasma concentration*
CP	*Chronic prostatitis*
DA	*Dopamine*
DH	*Dorsal horn*
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EAU	*European Association of Urology*
ED	*Erectile dysfunction*
EFT	*Emotion-focused therapy*
FDA	*Food and drug administration*
GABA	*Gamma-Aminobutyric acid*
GH	*Growth hormone*
ICD-10	*International classification of diserase 10th version*
IDDM	*Insulin-Dependent Diabetes Mellitus*
IELT	*The intravaginal ejaculation latency time*
ISSM	*The International Society for Sexual Medicine*
Kv4.3	*Potassium voltage gated channels*
MAOIs	*Monoamine oxidase inhibitors*
MEApd	*Posterodorsal part of the medial amygdala*

MPOA	*Medial preoptic area*
No	*Nitric oxide*
nPGI	*Nucleus paragigantocellularis*
NPT	*Nocturnal penile tumescence*
PAG	*Periaqueductal gray*
PDE5 inhibitors	*Phosphodiesterase type 5 inhibitor*
PE	*Premature ejaculation*
PEDT	*Premature Ejaculation Diagnostic Tool*
PEP	*Premature Ejaculation Profile*
PNpd	*The posterodorsal preoptic nucleus*
PROs	*Patient reported outcomes*
PTHrP	*Parathyroid hormone-related protein*
PVN	*Paraventricular nucleus of the hypothalamus*
SEG	*Spinal ejaculatory centre*
SNRIs	*Serotonin norepinephrine reuptake inhibitor*
SPFp	*Parvicellular subparafascicular nucleus*
SPN	*Spinal parasympathetic nucleus*
SSRIs	*Selective serotonin reuptake inhibitors*
T½	*Half-life*
TCAs	*Tricyclic antidepressants*
Tmax	*The time after administration of adrug to reach the maximum plasma concentration*
TPH	*Tryptophan hydroxylase*

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Premature ejaculation (PE) is the most common form of male sexual dysfunction. Globally, between 20% and 40% of men, at some point in their lives, have reported symptoms of PE or a complaint of PE.***(Porst et al; 2007)***.

Premature ejaculation (PE) may be classified as lifelong or acquired. Lifelong PE is characterized by early ejaculation in the majority of intercourse attempts with nearly every partner from the first sexual encounter onwards, whereas acquired PE develops at some point in a man's life after he has previously experienced normal ejaculation and may be linked to urological or psychological problems. ***(Waldinger; 2008).***

In(2006) Waldinger and Schweitzer proposed the existence of two other premature ejaculation syndromes, which have been called "natural variable premature ejaculation" and "premature-like ejaculatory dysfunction".

It is so difficult to get an accurate definition and diagnosis of premature ejaculation. Recently; The International Society of Sexual Medicine (ISSM) produced its guidelines of the diagnosis and management of PE. It postulated an evidence-based definition of PE and defined PE as "A male sexual dysfunction characterized by ejaculation which is always or nearly always occurs prior to or within 1 minute of vaginal penetration; and an inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual encounters". ***(Althof et al; 2009)***.

Premature ejaculation has been associated with erosion in sexual self-confidence and low sexual satisfaction in men and their female partners ***(Byers and Grenier; 2003).***

The Intravaginal Ejaculation Latency Time (IELT) is defined as the time from vaginal intromission to intravaginal ejaculation. ***(Waldinger et al; 2005)***

This measure unequivocally defines ejaculatory latency and has contributed to more objective research in men with and without PE. ***(Waldinger; 2007).***

Premature ejaculation up till now has no definitive etiopathology , investigation or effective treatment ***(Segraves et al; 2007).***

The etiology of premature ejaculation has included a diverse range of biogenic and psychological theories. Most of these proposed etiologies are speculative and not evidence based ***(McMahon; 2005).***

Treatment modalities include behavioral therapy and medical therapy ***(Richardson and Goldmeier; 2005).***

In 1956, urologist Semans described one of the earliest behavioral interventions, namely the "stop-start technique". A similar technique "squeeze technique" was proposed by sex therapists Masters and Johnson in 1970.***(Gurkan et al; 2008)***

A range of drugs are currently used by clinicians for the management of PE; antidepressants including Selective Serotonin Re-uptake Inhibitors (SSRIs), local anaesthetic agents and phosphodiesterase type 5 inhibitors.***(Mohee and Eardley; 2011)***

No therapy is approved by the FDA for treatment of PE ***(McCarty and Dinsmore; 2010).***

Dapoxetine is similar to the other SSRIs in that it exerts its effects through the inhibition of the serotonin reuptake transporter. ***(Hellstrom ; 2009)***

It has been statistically shown to significantly inhibit ejaculatory expulsion reflexes, acting at a supraspinal level. ***(Clement et al; 2007)***

There is evidence of its efficacy, its relatively mundane side effect profile and its validity as an on-demand medication. ***(Feige et al; 2011)***

Aim Of The work

The aim of this work is to evaluate the therapeutic role of Dapoxetine hydrochloride in treating primary premature Ejaculation with the therapeutic role of Tramadol hydrochloride through a single blinded placebo controlled study.

Physiology of ejaculation

Male sexual response comprises four phases: excitement including erection, plateau, ejaculation usually accompanied by orgasm and resolution. ***(Giuliano and Clèment, 2012).***

Ejaculation is defined as the expulsion of seminal fluid through the urethra and is closely associated with orgasm, extra genital response and subjective pleasurable feeling in men **(Coolen, 2004).**

There are three basic mechanisms involved in normal ante grade ejaculation: emission, ejection and orgasm **(McMahon *et al*, 2004).**

I- Emission

In emission the vas deferens, seminal vesicles and the prostate contract ejecting spermatozoa mixed with their products into the posterior

urethra, this occurs at high arousal. The bladder neck tightly closes to prevent retrograde flow. The external urethral sphincter also contract. The ejected products become entrapped in the prostatic urethra under high pressure (***McMahon, 2011).***

II- Ejection

During expulsion phase, smooth muscle fibers of the bladder neck contract to prevent semen to flow backward into the bladder. The pelvic floor muscles, with bulbospongiosus and ischiocavernosus muscles display stereotyped rhythmic contractions. The external urethral sphincter display intermittent closure and opening to propel semen in a pulsatile way distally throughout the external meatus ***(Colpi et al., 2004).***

The external urethral sphincter and pelvic floor striated muscles are solely commanded by the somatic nervous system. The trigger of rhythmic pelvic striated muscles contractions responsible for the expulsion of semen is still not clearly identified. It has been proposed that the expulsion phase of ejaculation is a reflex response to the presence of semen at high pressure in the prostatic urethra ***(Andersson and Abdel-Hamid, 2011).***

III- ORGASM:

It is sensory experience result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising from the veramontanum and contraction of the urethral bulb and accessory sexual organs **(McMahon, 2007).**

Orgasm is a complex neuro-psycho-physiological process that translates in intense cerebral discharge and physiological changes in the whole body ***(Giuliano, 2011).***