The Role of Penile Intracavernous injection therapy in patients with Erectile Dysfunction who failed treatment with oral sildenafil

Thesis
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In Urology

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List of Abbreviations

AVSST	**Audiovisual sexual stimulation tests**
BPH	**Benign prostatic hypertrophy**
CC	**Corpora cavernosa**
CCEMG	**Electromyography of the corpus cavernosum**
cGMP	**Cyclic guanosine monophosphate**
CS	**Corpus spongiosum**
DD	**Color duplex doppler sonography**
DHEA	**Dihydro-epiandrosterone**
DHEAS	**Dihydro-epiandrosterone stimulant**
ED	**Erectile dysfunction**
EDITS	**Erectile dysfunction inventory of treatment satisfaction**
FSH	**Follicular stimulating hormone**
HDL	**High density lipoproteins**
ICI	**Intracavernosal injection tests**
ICIT	**Intracavernous injection therapy**
IIEF	**International index of erectile function**
LH	**Leutenizing hormone**
MC	**Melanocortin**
NOS	**Nitric oxide synthase**
NPT	**Nocturnal penile tumescence**
PDE-٥	**Phosphodiesterase-٥**
PGE١	**Prostaglandin e١**
SHBG	**Sex hormones binding globulin**
SHIM	**Sexual health inventory for men**
SL	**Sublingual**
SNPs	**Single nucleotide polymorphisms**
TU	**Transurethral**
VSS	**Visual sexual stimulation**

Introduction and Aim of the work

INTRODUCTION AND AIM OF THE WORK

Introduction:

The inability of a male to attain and maintain an erection sufficient to allow sexual intercourse is called erectile dysfunction (ED). It is a part of the general male sexual dysfunction called impotence, which also includes libidinal, orgasmic and ejaculatory dysfunction. Until the ١٩٩٠'s, "impotence" was the term used in clinical work to refer to erectile dysfunction.

The most usual sexual dysfunction of man is weakness of erections. Erectile dysfunction affects millions of men, and although it may not mean a total loss of sexual satisfaction, it often creates a mental stress that affects the man's quality of life. Erectile dysfunction goes hand in hand with aging. **(*Feldman et al.*, ١٩٩٤)**.

Although the Greek and Romans appear to be pioneers in the field of describing the erotic life of the man behavior, this may be in some respects. But Egyptians had prepared the ground, around the banks of the Nile, erotic life flourished in ancient Egypt at all levels of society, contrary to what generally thought, it was recorded in words and pictures, the ancient Egyptians described impotence and recorded several methods to increase sexual power. In addition to magical spells, ancient Egyptians used aphrodisiacs of various kinds. They described

various medicines not only taken by mouth but also applied to the penis as a local remedy ***(Shokier and Hussien, ١٩٩٩)***.

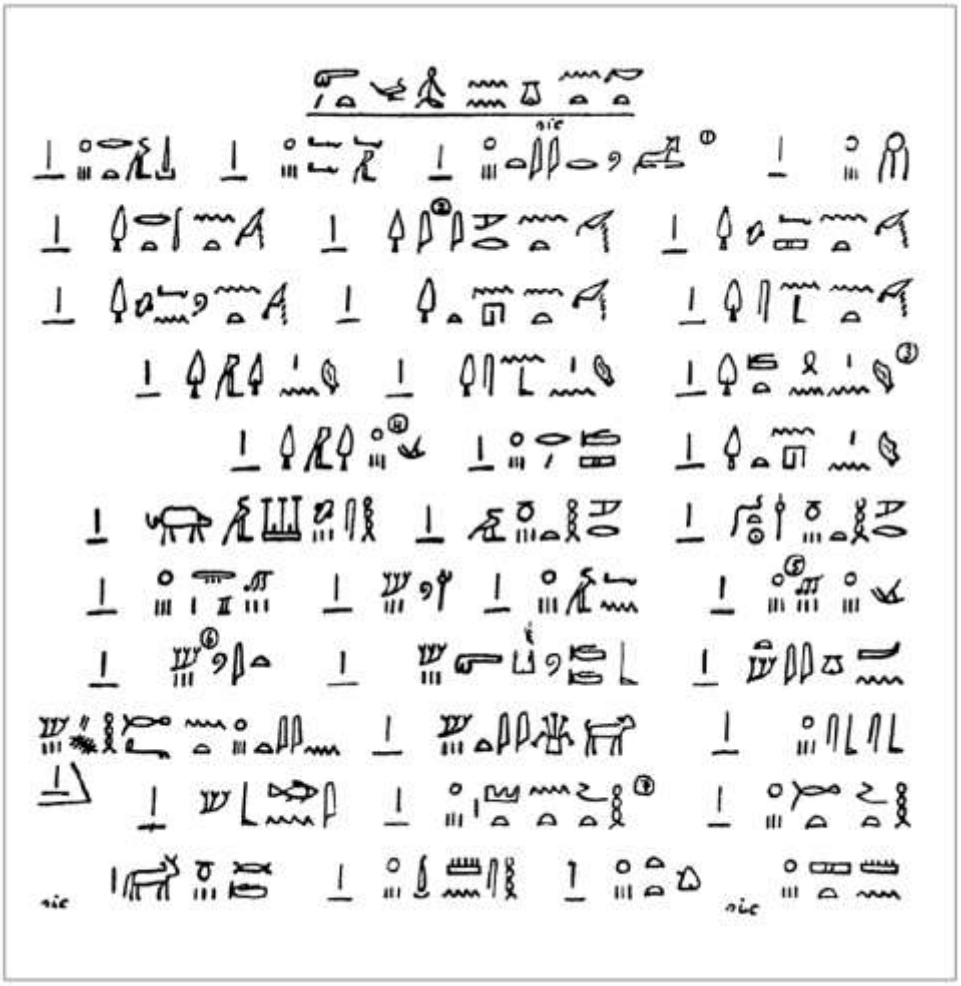

Figure ١: Prescription ٦٦٣ for "weakness of the male member" from Ebers Papyrus. ***(Ebbel, ١٩٧٣)***

Traditional Chinese medicine also had a role in prescribing acupuncture, vegetal, animal and mineral substance in the treatment of erectile dysfunction those have been undertaken for scientific research by western pharmacologists and

andrologists, some of these seem to be exceptionally efficacious in erectile dysfunction and impotence ***(Sergio and Hussein, ٢٠٠٥)***.

In ١٩٧٧, while performing a bypass procedure, a surgeon accidentally injected papaverine in the area near the penis. This produced a prolonged, fully rigid erection of ٢ hours' duration. Other medications such as Phenotolamine (Regitine) were noted to induce an erection in cats when administered intravenously. It wasn't until ١٩٨٢ the Dr. Virag, a surgeon in France, noted that the pressure inside the penis increased with an injection of papaverine ***(Virag, ١٩٨٢).***

Dr. Brindley, professor of Physiology at the Institute of Psychiatry in London, first reported that ١١ impotent men were able to have intercourse following an injection of vasoactive materials. Since then, the injection of medication into the penis for evaluation of erectile dysfunction has been one of the most popular as well as controversial topics in Urology. Although there has been a very rapid, widespread acceptance of medically induced erections over the last ٧ years, there are still several questions to be answered ***(Brindley, ١٩٨٦)***.

The mechanism of erection is also better understood now when the new drugs have been investigated. ***The clinical investigations of erectile dysfunction have become more sophisticated:*** color duplex Doppler (DD) sonography, audiovisual sexual stimulation tests (AVSST), and nocturnal penile tumescence (NPT) (Rigiscan device). It is also possible

to examine the etiology of erectile dysfunction with intracavernosal injection tests (ICI) ***(Stackl et al., ١٩٩٠)***.

Nowadays the most important contemporary treatments of ED are per-oral phosphodiesterase-٥ (PDE-٥) inhibitors and intracavernosal pharmacotherapy using vasoactive medicines. Seventy to ninety percent of all patients with ED are able to restore their erections with these treatments. However, these drugs are not suitable to every patient ***(Goldstein et al., ١٩٩٨)***.

After having experimented with over forty different types of medications, we presently use three: papaverine, phentolamine (Regitine) and prostaglandin E١.

Aim of the Work:

In our study we are tackling the patients who showed no response on the oral drug sildenafil and evaluating the role of different vasodilator materials used by self administered intracavernosal injection in the management of this group of patients. The efficacy, tolerability, side effects and cost effectiveness of these different materials; namely Prostaglandins E١ and Trimix (combined Prostaglandin E١, Phentolamine and Papaverine) will be discussed.

Review of Literature:

Anatomy of the penis & Physiology of erection

Epidemiology of Erectile Dysfunction

Pathophysiology of Erectile Dysfunction

Management of Erectile Dysfunction

Anatomy of the penis & Physiology of Erection

ANATOMY OF THE PENIS

AND PHYSIOLOGY OF ERECTION

Anatomical background:

The penis is composed of three cylindrical structures: the paired, dorsally positioned corpora cavernosa (CC) and the ventrally positioned corpus spongiosum (CS), which surrounds the urethra. Each structure is surrounded by its own fascial sheath, or tunica albuginea and all are surrounded by the outer Buck's fascia. The CC, primarily composed of venous sinusoids covered with smooth muscle cells, is the main structures responsible for erectile function and essentially serves as reservoirs for the storage of blood during erection. The paired internal pudendal arteries are the principal blood supply to the penis. These vessels arise from the internal iliac (hypogastric) artery and form the penile arteries, which, in turn, divide into three main branches. The bulbourethral artery supplies the CS, and the dorsal artery of the penis nourishes the penile skin and glans. The paired cavernous arteries, coursing through the center of the CC, are the principal blood supply to the erectile tissue and are important for corporal engorgement. It should be noted that there could be considerable variation in the penile arterial supply. The principal venous drainage of the CC is the subtunical and emissary veins, which drain into the deep dorsal vein, while the superficial dorsal vein provides for cutaneous drainage of the penis. The other major venous

drainage system is the cavernous and crural veins, which form the pudendal vein. The venous drainage of the penis is also complex and variable.

The penis receives both somatic and autonomic (sympathetic and parasympathetic) innervations. The somatic component (S^{2} to S^{4}) is the dorsal nerve of the penis, a terminal branch of the pudendal nerve carrying penile sensory afferent fibers. Sympathetic (T^{10} to L^{2}) and parasympathetic (S^{2} toS^{4}) fibers form the pelvic plexus and cavernosal nerves. These fibers run posterior and lateral to the tips of the seminal vesicles and prostate, and penetrate the genitourinary diaphragm at the ٣ and ٩ o'clock positions. The nerves are located at the ١ and ١١ o'clock position relative to the bulbar urethra before entering the CC. Cholinergic parasympathetic fibers are the primary neuronal system involved in the erectile process and are involved in both tactile and psychogenic erection. The role of the sympathetic nervous system is less defined. It is generally agreed that adrenergic stimulation results in penile detumescence; however, sympathetic fibers may have a role in psychic erection ***(Benson and Boileau, ١٩٩٩)***.

Recent evidence also points to the presence of non-cholinergic, non-adrenergic neurons in the CC that cause penile tumescence through release of an endothelium-derived relaxation factor, nitric oxide. This compound, which is also released in response to cholinergic stimulation, is believed to be

the principal mediator of CC smooth muscle relaxation. Nitric oxide appears to exert its effect through increased intracellular levels of cyclic guanosine monophosphate (GMP). With cavernosal artery smooth muscle relaxation, blood engorges the sinusoids resulting in tumescence. To maintain an erection, the corporal venous outflow has to be occluded. When the CC engorges with blood, they enlarge and stretch the surrounding tunica albuginea. This, in turn, compresses the small venules running through the tunica and blocks the venous outflow of the penis. Corporal smooth muscle constriction and the opening of venous channels allows for drainage of corporal blood resulting in detumescence (Fig ٢) ***(Carrier et al., ١٩٩٣)***.

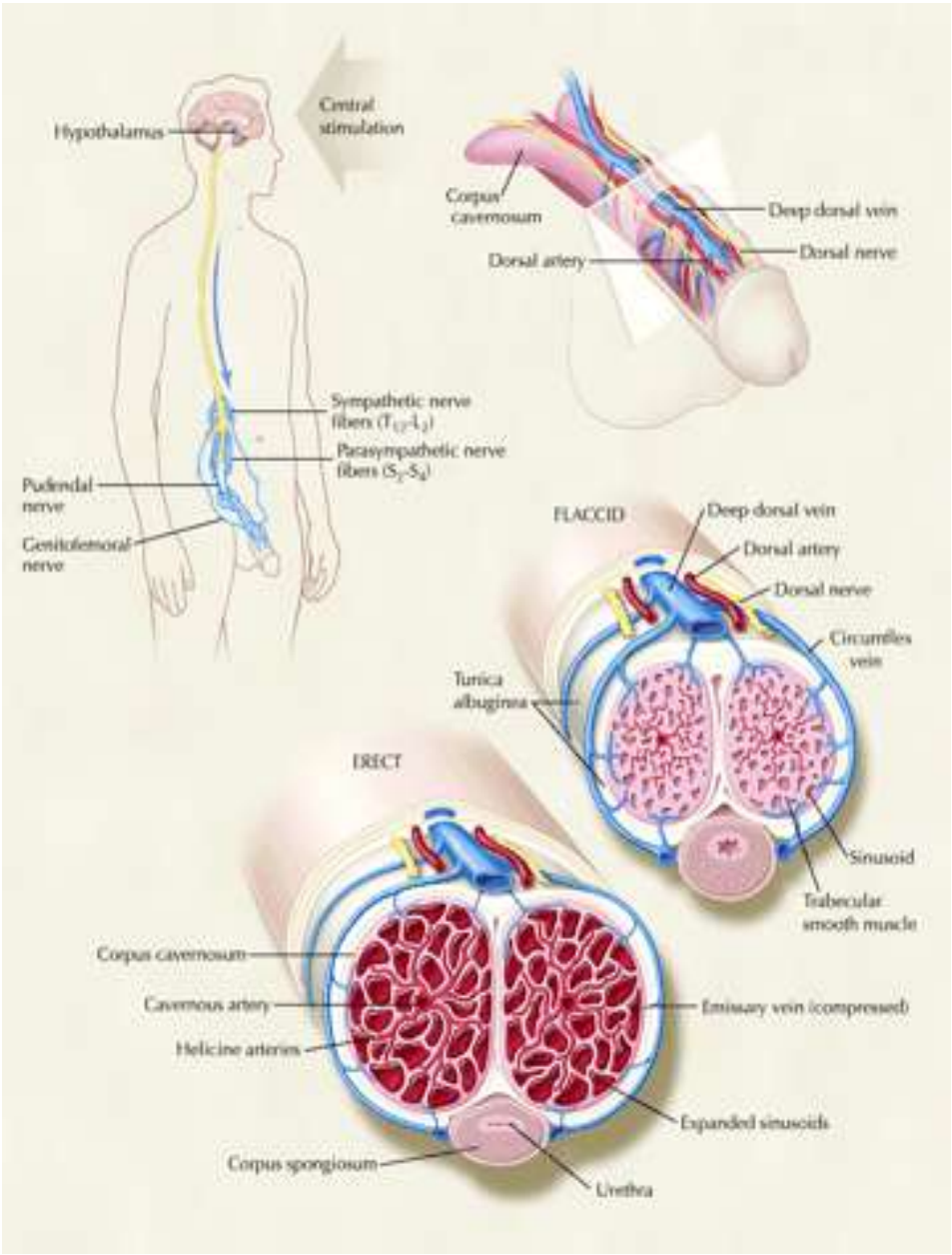

Fig. ٢: Cross sectional view of the penis ***(Jean et al., ٢٠٠٤)***

Physiological background of Erection:

Penile erection is a hemodynamic process initiated by the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, nitric oxide is released from nerve endings and endothelial cells in the corpus cavernosum. Nitric oxide activates the enzyme guanylate cyclase, which increases synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum. The cGMP triggers smooth muscle relaxation, allowing increased blood flow into the penis, resulting in an erection.

The tissue concentration of cGMP is regulated by the rates of both synthesis and degradation via phosphodiesterases (PDEs). The most abundant PDE in the corpus cavernosum is the cGMP-specific phosphodiesterase type ٥ (PDE-٥); therefore, the inhibition of PDE-٥ enhances erectile function by increasing the amount of cGMP. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE٥ has no effect in the absence of sexual arousal (fig.٣, ٤) ***(Lue, ٢٠٠٠)***.