European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 07, Issue 11, 2020

A Comparative Pilot Study on The Effect of Intracavernosal Injection Of (Papaverine/Verapamil) And (Papaverine/Phentolamine) In Erectile Dysfunction Patients

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Abstract
Background: Intracavernosal injection (ICI) as a locally acting therapeutic modality has been tried since early 70s for the treatment of ED. Several vasoactive substances have been tried either a mono-therapy or in combination (i.e. Bimix or Trimix); whereas most of those mixtures were Papaverine based. Verapamil as a calcium channel blocker possess a vasodilator effect, thus it has been tried in very few trials as ICI either alone or in combination with Papaverine. In another perspective, verapamil was found to have anti-fibrotic properties; therefore it could have a dual benefit besides being a vasodilator.
Methods: Hereby, our study was conducted trying to assess the effect of ICI of Papaverine/Verapamil mixture on penile erection as well as penile hemodynamics, compared to the traditional Bimix (i.e. Papaverine/Phentolamine) among a subgroup of PDE5I nonresponders (n=50).
Results: Our results showed that there was statistically significant difference while comparing both mixtures (Papaverine/Phentolamine) vs (Papaverine/Verapamil) concerning IIEF-5, cavernosal artery dilatation, PSV and RI with P-values (0.001, 0.003, 0.006 and 0.003) respectively.
Conclusion: Therefore, a bi-mixture of (Papaverine/Verapamil) could be a promising combination for treatment of ED via ICI with its dual-effects as cavernosal smooth muscle relaxant causing erection as well as anti-fibrotic properties.

Key words: *Erectile dysfunction (ED); Intracavernosal injection (ICI); Papaverine; Phentolamine; Verapamil.*

INTRODUCTION

Erectile dysfunction (ED) is defined as the recurrent or persistent inability to obtain and/or maintain penile erection of good quality sufficient for satisfactory coitus [1]. Many causes have been attributed to ED that could be classified into organic, psychogenic or mixed causes. In the past, erectile dysfunction was considered to be a purely psychogenic disorder,

but current evidence suggests that more than 80% of cases have an organic etiology [2]. Several treatment modalities have been implemented in the last few decades including; psychosexual therapy, oral PDE5 inhibitors, intracavernosal injections (ICI), medicated urethral system for erection (MUSE), external vacuum devices, and finally penile prosthesis [3, 4].

ICI of vasoactive drugs is considered as tool for diagnosis as well as treatment of ED. Several vasoactive agents have been tried; however the most well studied agents were papaverine, phentolamine, prostaglandin E1, either as mono-therapy or their mixtures. It is to be mentioned that ICI could have some short-term side effects such as priapism and penile pain, while long-term side-effects include cavernous fibrosis [5, 6]. However, many clinical trials have been conducted trying to find more novel vasoactive agents to be used as ICI for treatment of ED including; sodium nitroprusside, verapamil, calcitonin-gene-related-peptide (CGRP), linsidomine (syn. SIN-1), vasoactive intestinal polypeptide (VIP) [7, 8].

Verapamil is basically an anti-hypertensive agent belonging to calcium channel blockers of the phenyl alkylamine class. It acts by blocking Ca^{+2}channels, resulting in relaxation of vascular smooth muscles, and leading to blood vessel dilatation [9, 10]. By far, verapamil is used a therapeutic agent for treatment of peyronie's disease via intralesional injection [11, 12], however very few clinical trials either in vitro or in vivo (animal or human) have been mentioned in literature concerning its use in treatment of ED. Whereas, the first human clinical trial was conducted by **Bolayir and Gökşin** [13] for the use of ICIs of (Papaverine 30 mg /Verapamil 5 mg) on males complaining of ED. This mixture was found to be tolerable and effective among the studied subjects.

IIEF-5 was used as a method of objective assessment (i.e. baseline at initial assessment and after using both mixtures for self-injection at home) as well as subjective assessment through penile duplex study to assess cavernosal artery dilatation as well as penile hemodynamics (PSV, EDV and RI) while evaluating the effect of intracorporeal injection (ICI) of (Papaverine 30 mg/Verapamil 5 mg) in comparison to the traditional bi-mixture (Papaverine 30 mg/ Phentolamine 1 mg).

METHODS

Inclusion and exclusion criteria

A total of (50) were recruited from the Andrology outpatient clinic. All recruited patients in this prospective pilot study were 40 to 70 years old and had been suffering from ED for at least 6 months and failed to respond to PDE5Is. Other patients who suffered from uncontrolled medical conditions (e.g. diabetes mellitus, dyslipidemia, arrhythmias, hepatic failure, chronic renal failure, heart failure or neurogenic illness) as well as hypogonadism were excluded from the study. Moreover, heavy smoking (smoking index ≥ 400), alcohol or drugs abuse, or any other drugs that may affect erectile function and patients with Peyronie's disease or urogenital operations were also excluded from the study.

Clinical assessments

Initially, all participants were subjected to full history taking (personal history including special habits of medical importance, sexual history, medical and surgical history) , as well as initial assessment of erectile function by the Arabic validated version of International index of erectile function (IIEF-5) as a standardized method for assessment of erectile dysfunction [14]

Besides that, tedious clinical assessment both general and local genital examination were performed to exclude clinical hypogonadism, urogenital anomalies or Peyronie's disease. Notably, all selected subjects had their laboratory investigations including, glycated hemoglobin (HBA1c), lipid profile, serum total testosterone levels were within normal ranges excluding false non-responsiveness.

Penile colour duplex Doppler ultrasound (CDDU) assessment

Afterwards, all patients were subjectively assessed with penile color duplex Doppler ultrasound (CDDU) using both ICI mixtures as follows; first visit using ICI (Papaverine 30 mg /Phentolamine 1mg), followed by a wash out interval of at least two weeks for each subject followed by second visit repeating the exact previous procedures using ICI (Papaverine 30 mg / Verapamil 5 mg). It is to be mentioned that after each visit the patients were given a single dose of each mixture for use as a home therapy, and then the IIEF-5 scoring was recorded. Notably, the doses used for self-injection at home were the same used for penile duplex assessment (Papaverine 30 mg/ Phentolamine 1 mg), and (Papaverine 30 mg/ Verapamil 5mg).An ultrasound machine (Mindray Z5, Shenzhen Mindray Bio-Medical Electronics Co., China) with linear probe (7.5-10 MHz) frequency was used to assess degree of dilatation of cavernosal arteries as well as penile hemodynamics (i.e. Peak systolic velocity (PSV), End diastolic velocity (PSV), and Resistive index (RI)). Readings were taken from the proximal parts of cavernosal arteries post-injection of ICI at timely intervals (5, 10, 15, and 20 minutes). The standard normal values of penile hemodynamics were according to ISSM standards of practice (SOP) as follows; PSV > 30 cm/second, venous flow < 3 cm/second, and RI > 0.8 [15].

Statistical analysis

By the end of the study, all collected data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data were summarized using mean, standard deviation, median, minimum, and maximum in quantitative data. Comparisons between quantitative variables were done using the nonparametric Mann–Whitney test. For comparison of serial measurements within each patient, the non-parametric Wilcoxon signed-rank test was used. A p-value of less than 0.05 was considered as statistically significant [16].

RESULTS

Our study included (50) male subjects who were suffering from ED not responding to PDE5Is (true non-responders) for at least 6 months, whereas the mean duration of ED was 4.90 ± 2.87 years. The age of all selected patients ranged from 40 to 70 years with mean age was 52.58 ± 8.75 years. The associated comorbidities were as shown in ***table (1)***. On the

other hand, the laboratory values of risk factors at initial assessment of the patients were summarized in ***table (2)***.

Table (1): Distribution of associated co-morbidities (smoking, diabetes, and CV risk) in study group

Associated co-morbidities n (%)	
Smoking	**No** 11 (22.0 %) : **Yes** 39 (78.0 %)
Diabetes	**No** 22 (44.0 %) : **Yes** 28 (56.0 %)
CV risk	**No** 18 (36.0 %) : **Yes** 32 (64.0 %)

Table (2): Laboratory values (Lipid profile, HbA1c and total testosterone) at initial assessment of the patients

Cases (n=50)	Mean	SD	Minimum	Maximum
Cholesterol (mg/dL)	165	17.32	123	198
Triglycerides (mg/dL)	123	14.20	98	147
LDL (mg/dL)	75.30	10.30	58	95
HDL (mg/dL)	82.40	8.04	65	100
HbA1c (%)	5.53	0.57	4.50	6.60
Testosterone (total) (ng/mL)	4.87	0.80	3.50	6.50

In our study, the mean of baseline IIEF-5 score of all patients was 3.82±1.57. On the other hand, the IIEF- score after using both mixtures for home therapy using (Papaverine/Phentolamine) was 11.03±3.04, while it was 13.65±4.30 using (Papverine/Verapamil) mixture and that showed statistically significant difference with p-value 0.001 as shown in **table (3).**

Table (3): IIEF-5 scores after using ICI bi-mixtures of (Papaverine/Phentolamine) versus (Papaverine/Verapamil) for home therapy.

IIEF-5	Papaverine/Phentolamine	Papaverine/Verapamil	P value
Mean	11.03	13.65	0.001
SD	3.04	4.30	
Minimum	6.00	6.00	
Maximum	17.00	21.00	

Concerning the mean cavernosal artery diameters, it was found to be 0.85±0.10 using (Papaverine/Phentolamine), while it was 0.92±0.09 with (Papverine/Verapamil) and that showed statistically significant difference with p-value 0.003 as shown in **table (4)**.

Table (4): Mean Cavernosal artery diameters using (Papaverine/Phentolamine) versus (Papaverine/Verapamil)

Cavernosal artery diameters (mm)	Papaverine/Phentolamine	Papaverine/Verapamil	P value
Mean	0.85	0.92	0.003
SD	0.10	0.09	
Minimum	0.70	0.70	
Maximum	1.00	1.1	

On the other hand, evaluation of penile hemodynamics of the subjects while using both mixtures showed statistically significant difference concerning the PSV and RI with p-values 0.006 and 0.003 respectively. However, there was no statistical difference between both mixtures concerning the EDV with p-value 0.315 as shown in **table (5)**.

Table (5): Penile hemodynamics (PSV, EDV and RI) using (Papaverine/Phentolamine) versus (Papaverine/Verapamil)

ICI	Papaverine/Phentolamine				Papaverine/Verapamil				P value
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	
PSV (cm/sec)	41.25	20.63	17.80	98.70	57.60	22.62	23.20	112.90	**0.006**
EDV (cm/sec)	**1.11**	**1.43**	**0.01**	**4.10**	**0.78**	**1.62**	**0.01**	**4.70**	**0.315**
RI	**0.69**	**0.19**	**0.40**	**1.00**	**0.82**	**0.18**	**0.40**	**1.20**	**0.003**

Interestingly, no prolonged erections or priapism have been encountered in any of the patients who had received (Papaverine/Verapamil) mixture. Whereas, nine patients had experienced priapism when subjected to ICI with (Papaverine/Phentolamine), that required evacuation.

DISCUSSION

The present study included a total of (50) married male patients suffering from ED with no response to PDE5-I scheduled for penile duplex study to evaluate the effect of ICI of (Papaverine / Phentolamine) and comparing it with (Papaverine / Verapamil). All subjects were initially assessed by baseline IIEF-5 score. Afterwards, the penile hemodynamics (PSV, EDV, RI and cavernosal artery diameter dilatation) were evaluated through penile duplex study using both bi-mixtures in two different visits. Moreover, the patients were given a single dose of ICI of each mixture as self-injection to try at home; thereafter they were assessed for the degree of erection improvement using IIEF-5 scoring. Up to our knowledge, this study is considered as the second in vivo human trial as well as the first in evaluating the effect of this bi-mixture both subjectively and objectively.

As early as, ***Brindley*** [17] had conducted a preliminary study on ICI of different vasoactive agents and he reported that some drugs exhibited a potential ability to relax smooth muscle, including verapamil, caused partial erection [17]. Few years later, some *in vitro* animal and human trials were conducted to clarify the relaxant effect of calcium channel blockers, and they concluded that verapamil could be a potential erectogenic agent [18, 19].

Later on, ***Bolayir and Gökşin*** [13] had conducted a clinical trial evaluating the ICI of a bi-mixture of (Papaverine 20 mg / Verapamil 5 mg) on (40) males complaining of ED. Patients' age was between 40 and 75 years. Interestingly, among those patients no priapism was encountered and fibrosis was reported in one patient. Their study concluded that this bimixture was found to be reliable, well accepted with minimum local risks among ED patients.

In the same perspective, an animal model trial was conducted by ***Sarikaya et al.*** [20] on the effects of various intracavernously injected calcium channel blockers and papaverine in dogs, and investigated their clinical applications. They administered papaverine 30 mg, nifedipine 10 mg, nitrendipine 10 mg and verapamil 2.5 mg to ten adult dogs intracavernously, in different occasions.

All dogs were evaluated by assessing intracavernous pressure values, systemic blood pressure (SBP) and heart rate (HR) values after the ICI of the different drugs. They found that Papaverine induced full erection in all of the ten dogs, whereas nifedipine induced full erection in 4, nitrendipine in 5 and verapamil in 6 out of the 10 dogs. Besides that, nifedipine and nitrendipine caused significant decreases in SBP and increases in HR compared to verapamil and papaverine. Finally, they concluded that the effects of ICI of calcium channel blockers were not superior to those of papaverine when used as a single agent. In addition, they did not recommend nifedipine and nitrendipine for intracavernous injection due to their systemic side effects on SBP and HR. However, they stated that verapamil could be a promising therapeutic vasoactive agent via ICI as mono-therapy or may be used as a combination therapy [20].

Our results showed that, the increase in cavernosal artery diameter among (Papaverine / Verapamil) group was higher than that in (Papaverine / Phentolamine) group, and the difference was statistically significant with a P-value (0.003). Concerning the PSV measured at 5 min, it was found to be higher in (Papaverine / Verapamil) compared to the other group, and the difference was statistically significant with a P-value (0.006). On the other hand, the EDV measured at 20 min was showed no statistically significant between both groups with a P-value (0.315).Additionally, the RI after ICI in the (Papaverine / Verapamil) group was found to be higher than the other group and the difference was statistically significant with a P-value of 0.003.

Our results agrees with the findings found with almost the only clinical human study conducted by ***Bolayir*** and ***Gökşin***[13] that no priapism was encountered when ICI was done to their 40 male patients while using (Papaverine 30 mg/ Verapamil 5 mg), despite the fact that ***Bolayir*** and ***Gökşin***[13] used a dose of (Papaverine 20 mg/ Verapamil 5 mg)**.** Besides that, verapamil is considered as a therapeutic agent for the treatment of early (non-calcific) Peyronie's disease through intralesional injections either alone or in combination with steroids. Its anti-fibrotic properties were attributed to the increase in extracellular collagenase activity, decreased metabolic activity of fibroblasts, extracellular collagen deposit reduction, as well as inhibition of calcium deposition [21, 22]. Although combined intracavernosal verapamil injection was not confirmed as sufficient to prevent fibrosis in the short term, its beneficial histological effect should be further evaluated on a highdose and long-term scale [23].

CONCLUSIONS

Verapamil could be considered as a promising erectogenic drug that may be used in treatment of ED via the ICI route as it possesses dual action through smooth muscle relaxation resulting in penile erection as well as its anti-fibrobalstic activity. Thus, this mixture of (Papaverine/Verapamil) could be safer and effective for the treatment of ED especially in those with minimal degrees of fibrosis. Finally, we recommend further studies to evaluate the long

term effects and side effects of (Papaverine/Verapamil), besides modifying study design into double blind, cross over, placebo controlled fashion as well as increasing sample size and follow up of patients on home therapy concerning sexual satisfaction and monitoring long term effects.

Conflict of interest

No conflict of interest to be declared by all authors.

Abbreviations

ED: Erectile dysfunction**; EDV:** End diastolic velocity**; HbA1c:** Glycated hemoglobin**; HR:** Heart rate**; ICI:** Intracavernosal injection; **IIEF-5:** International Index of Erectile Function (5- items version); **PDE5:** Phosphodiestrase type-5; **PSV:** Peak systolic velocity; **RI:** Resistive index; **SBP:** Systemic blood pressure.

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