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PII: S0090-4295(20)31188-2
DOI: <https://doi.org/10.1016/j.urology.2020.09.030>
Reference: URL 22553

To appear in: *Urology*

Received date: 26 June 2020
Revised date: 17 September 2020
Accepted date: 20 September 2020

Please cite this article as: Mahmoud A. Bassiem , Iman Y. Ismail , Tarek A. Salem , Ahmed I. El-Sakka , Effect of Intracavernosal Injection of Prostaglandin E1 on Duration and Rigidity of Erection in Patients with Vasculogenic Erectile Dysfunction: Is it Dose Dependent?, *Urology* (2020), doi: <https://doi.org/10.1016/j.urology.2020.09.030>



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Effect of Intracavernosal Injection of Prostaglandin E1 on Duration and Rigidity of Erection in Patients with Vasculogenic Erectile Dysfunction: Is it Dose Dependent?

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-Runninghead: Effect of PGE1 on Duration and Rigidity of Erection

-Keywords: PGE1, Erectile Function, Penile Rigidity

-Word counts: 2819

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Objective: To assess if the effect of intracavernosal injection (ICI) of prostaglandin E1 (PGE₁) on duration and rigidity of erection is dose dependent in patients with different types of vasculogenic erectile dysfunction (ED)?

Methods: A hundred patients with ED were assigned into 4 groups (n=25/each); group (A) patients with arteriogenic ED, group (B) patients with veno-occlusive ED, group (C) patients with mixed (arteriogenic and veno-occlusive) ED and group (D) patients who have only psychogenic ED (control). After ICI of PGE₁ patients were assessed using penile doppler ultrasonography and erection hardness score together with calculation of erection duration. The starting dose of PGE₁ was 5µg which was increased to 10µg and 20µg as a maximal dose when needed.

Results: The mean PSV of patients in groups A, B, C and D were 24.38±3.3, 37.74±8.28, 22.24±3.85 and 47.76±6.27 respectively. In group D, 88% have achieved the best response at dose of 5 µg while 5.3%, 21.7% and 0% have achieved the best response at dose of 5µg in groups A, B and C respectively (p<0.05 for each). The rest of patients have required either 10 or 20 µg to achieve the best response. Patients in group C have required the highest dose of PGE₁ to achieve the best response (p<0.05).

Conclusion: Intracavernosal injection of PGE₁ in escalating doses have improved the rigidity and duration of erection in patients with different types of vasculogenic ED. Patients with mixed arteriogenic and veno-occlusive ED have required the highest dose of PGE₁ to achieve the best response.

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Journal Pre-proof

Introduction:

Vasculogenic ED is the most common type of organic ED and can be caused by arterial insufficiency, veno-occlusive dysfunction, or a combination of arterial insufficiency and venous leak (1). Several reports in the early 1980s concerning intracavernosal injection (ICI) of papaverine and phenoxybenzamine have opened the door to a new era in the diagnosis and treatment of ED. Virag and Adaikan demonstrated the ability of intracavernously injected prostaglandin E₁ (PGE₁) to induce penile erection (2), and it was proven to be the safest vasoactive agent, as well as an effective one (3).

Alprostadil was FDA approved in 1994 and its high efficacy and low side effect rates prompted the clinical guidelines panel on ED of the American Urological Association (4) and several consequent studies (5,6) to recommend that alprostadil monotherapy should be preferred to other vasoactive drugs in self-injection therapy.

Furthermore, ICI together with penile Doppler ultrasound helps to detect vascular abnormalities and to differentiate between the vasculogenic causes of ED (7). Men with different underlying ED etiologies showed variable responses to ICI with improvement of erection duration and rigidity in association with higher doses of vasoactive agents. The strongest response was reported in the patients with neurogenic ED (8), while the lowest response was reported in the patients with veno-occlusive dysfunction (9).

Various existing examinations are widely used for the evaluation of vascular ED, they still have some shortcomings, such as invasiveness, contingency, high false positive rate (10). Although improvement of erectile response with increase doses of ICI of vasoactive agents has been reported in previous studies; however, the improvement of erection duration and rigidity in association with ICI of PGE₁ was not thoroughly investigated in patients with different types of vasculogenic ED. Further, evaluation of the response to ICI of PGE₁ in each type of vasculogenic ED in comparison to psychogenic ED was not settled yet.

This prompted us to investigate the dose effect of PGE1 in optimization of erection duration and rigidity in patients with different types of vasculogenic ED which could be of clinical merit.

Materials and Methods:

A hundred patients with different etiology of ED for at least six months who attended the urology clinic at XXXX Hospital from July 2017 throughout June 2018 were recruited to this prospective study. Participants were assigned into 4 groups according to penile color Doppler ultrasound (CDU) (n=25/each); group (A) patients with arteriogenic ED, group (B) patients with veno-occlusive ED, group (C) patients with mixed (arteriogenic and veno-occlusive) ED and group (D) patients who have only psychogenic ED as a control group. Patients with hormonal or neurogenic causes of ED, history of priapism or priapism predisposing factors (leukemia, polycythemia, sickle cell anemia), anatomical abnormalities such as Peyronie's disease were excluded from the study.

Baseline assessment:

All patients were subjected to: detailed medical and sexual history, a complete physical examination and routine laboratory investigation including total testosterone and prolactin assessment. International index of erectile function (IIEF-5) was used to assess ED. The erectile function domain consists of questions 1-5 and question 15 for assessing the global erectile function. Scoring the IIEF domain of erectile function allowed the classification of each patient as having no (26-30), mild (17-25), moderate (11-16) or severe (0-10) ED (11).

Assessment of erection rigidity and duration:

After ICI of PGE1 (Caverject, Pfizer, New York, NY, USA) erection was assessed using erection hardness score (EHS) (12) and also calculation of erection duration (the time from the start till the end of erection) (9,13). The starting injection dose of PGE1 was 5 µg which was increased to 10 µg and to 20 µg as a maximal dose when needed. If patient has achieved the best response (grade 4 erection for at least 15 minutes) at any dose, the procedure was stopped and no further doses were administrated. If patient has not achieved the best response the subsequent dose was not administered less than 3 days and not more than 14 days apart.

Color Doppler ultrasound (CDU):

Assessment of the penile vasculature was achieved using CDU with 7.5 MHz probe (Simens, GM-6600A2E00). After ICI of PGE1 patients were allowed 5 minutes for manual self-stimulation. Then CDU recording of the cavernous arteries was performed along an arterial segment corresponding to a Doppler angle of 60 and sample volume of 2 mm in all patients to obtain comparable data among them. The Doppler parameters, peak systolic velocity (PSV), end diastolic velocity (EDV) and the resistive index (RI) were recorded after ICI if the patients had achieved the best response or had received the maximal dose with/out best response.

Definitions:

- Start of erection: 20% increase in penile diameter;
- End of erection (detumescence): when the penile diameter returned to the starting value;
- Duration of erection: the time from the start till the end of erection (9,13).
- The best response: grade 4 erection that lasted at least 15 minutes

-Arteriogenic ED was diagnosed when PSV is lower than 35cm/sec.

-Veno-occlusive ED was diagnosed when EDV is higher than 5 cm/sec and RI is lower than 0.9.

-Mixed arteriogenic-veno-occlusive ED was diagnosed when PSV is lower than 35cm/sec and in concomitant with EDV is higher than 5 cm/sec.

The institutional research and ethical committee (Institution Review Board) had reviewed and approved the study. Each patient had provided an informed consent.

Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS® ver.21.0) software program (SPSS, Inc., Chicago, IL, USA). Chi-square test was used to compare categorical variables. Kruskal-Wallis H test was used to compare median of IIEF and ED duration. Mann-Whitney U test was used to compare two means of non-normal distribution variables. Student's t test was used to compare two means normal distribution variables. ANOVA was used to compare means of more than two variables of normally distributed parameters of ED severity and duration, EHS and Doppler parameters. A *p* value <0.05 was considered statistically significant.

Results:

Sociodemographic data:

A hundred patients were recruited to this study. The mean age \pm SD of the study population were 53.2 \pm 6.5, 50.8 \pm 7.3, 52.7 \pm 8.9, and 34.2 \pm 8.6 in groups A, B, C and D respectively. No significant difference among groups A, B and C regarding age (*p* > 0.05 for each). Group D had

statistically significant lower number of medical co-morbidities than others groups ($p<0.05$ for each). Risk factors and medical co-morbidities (BMI, DM, hypertension) were more prevalent in groups A, B and C in comparison to group D ($p<0.05$ for each). No significant difference in smoking among the study groups, $p=0.434$ **Table (1)**

Erectile function assessment:

ED duration: The medians of ED duration were 24, 18, 20 and 6 months in group A, B, C and D respectively. Patients in group D have statistically significant shorter ED duration than groups A, B and C ($p<0.05$ for each). (Table 2 a)

IIEF Score: The means of IIEF score were 15 ± 2 , 14 ± 5 , 11 ± 5 and 20 ± 4 in groups A, B, C and D respectively. Group C has a significant lower IIEF score than other groups ($p<0.05$ for each). Group D has significant higher IIEF score than other groups ($p<0.05$ for each), (Table 2 a, b).

Doppler parameters variables:

The means PSV of patients in groups A, B, C and D were 24.38 ± 3.3 , 37.74 ± 8.28 , 22.24 ± 3.85 and 47.76 ± 6.27 respectively. Group D has statistically significant higher PSV than other groups while groups A and C have significant lower PSV than other groups. ($p<0.05$ for each), (Table 2 a, b). Pairwise comparisons among studied groups revealed that patients in group D have significant lower EDV and significantly higher RI than other groups ($p<0.001$ for each), (Table 2 a, b).

Best response according to doses and erection duration:

Of patients, 76%, 92%, 76% and 100% have achieved the best response throughout the study in groups A, B, C and D respectively. In group D, 88% of patients have achieved the best response at dose of 5 μg while 5.3%, 21.7% and 0% have achieved the best response at dose of 5 μg in

groups A, B and C respectively. The differences between patients in group D and other groups were significant ($p < 0.05$ for each), (Table 3 a). The rest of patients have required 10 or 20 μg to achieve the best response. The means of erection duration were 14.8, 16.2, 11.8 and 27.6 minutes in groups A, B, C and D respectively with significant differences between groups ($p < 0.05$ for each), (Table 3 a, b). Patients in group C have required the highest dose of PGE₁ to achieve the best response in comparison to other groups ($p < 0.05$ for each), (Table 3 a, b).

No patients had developed significant post ICI complications. Minor hematoma at the site of injection was developed in two patients which has resolved spontaneously. Only one patient with psychogenic ED has developed prolonged erection that resolved in less than 4 hours conservatively.

Comment:

Intracavernosal injection therapy was considered the first-line treatment for ED until the introduction of oral phosphodiesterase type 5 inhibitors (PDE5I) in 1998 (14). However, it is still the second-best choice treatment option in men who do not respond to oral treatment or have contraindications for PDE5I treatment (15). Virag and Adaikan demonstrated the ability of ICI of PGE₁ to induce penile erection, and it was proven to be the safest vasoactive agent, as well as an effective one (2).

The main objective in the current study was to optimize the use of ICI of PGE₁ in improvement of erection rigidity and duration in patients with different types of vasculogenic ED. One hundred patients complaining of ED, of them 75 patients were diagnosed as having vasculogenic ED in addition to 25 patients with psychogenic ED as control group were recruited to this prospective study. Different ICI doses of PGE₁ in escalating pattern were started with a dose of 5 μg which was increased to 10 μg and 20 μg as a maximal dose according to the patient

response. This study clearly demonstrated that variable responses to ICI in terms of improvement of erection duration and rigidity have achieved in response to higher doses of PGE₁ in patients with vasculogenic ED. The best response was achieved in patients with solely arteriogenic or veno-occlusive ED and the lowest response was obtained in patients with mixed (arteriogenic and veno-occlusive) ED.

Several studies have tried to evaluate the dose dependent response of ICI of PGE₁ and have recommended the use of low doses of PGE₁ for the treatment of ED in order to reduce the incidence of side effects which were demonstrated to be dose-dependent (9,16-18). However, evaluation of the response in each type of vasculogenic ED in comparison to psychogenic ED was not settled yet.

In present study, ED patients received ICI of PGE₁ in escalating pattern, only patients with arteriogenic, veno-occlusive and mixed ED required to receive the maximum dose of 20 µg while none of psychogenic patients received this dose. Pairwise comparisons revealed all groups of vasculogenic ED have statistically significant shorter duration of erection than psychogenic ED group. On reaching 20 µg dose, the relation between the escalated doses and both rigidity and duration of erection have proven to be linearly positive. In line with our study, Stackl et al reported that 80% of the patients have a good response to 10 to 20 µg of PGE₁ but their study did not determine the lowest effective dose (19).

Previous study on 20 patients with psychogenic ED showed significant dose-response of PGE₁ for the grade of erection, onset and duration of erection. Full erection occurred in 50% of patients after the 5µg dose and in 85% after the 10µg dose (16). Another study on 16 men with vasculogenic ED showed dose dependent response to escalating doses of PGE₁ from 2.5 to 20 µg,

however, at greater than 20 μg a plateau was reached, indicating a nonlinear response. The effects of PGE_1 appear to be receptor dependent since larger amounts offer little additional benefit (18).

In a prospective, single-blind, dose-escalating study of PGE_1 on 20 men with ED of various etiologies, more than 70% of patients achieved rigidity with 5 μg or less and more than 80% had a full erection with 20 μg . Another study has reported a lower starting dose of 2.5 μg with escalation until the lowest effective dose is achieved (17). However, a dose of 2.5 μg is too low especially in patients with vasculogenic ED. In consistent with the current study, previous study has shown that, men with vascular etiologies required the largest maintenance dosage of 20 μg in comparison to neurogenic group who required a dose of 5 μg (20).

There were differences in penile Doppler parameters among various studies. Sikka et al, in their standard operating procedures study reported different assessment values of PSV and EDV, the RI measurements, according the diagnosis of the patient's penile vascular status: nonvascular, partial arterial, arterial, partial venous, venous, borderline mixed, or mixed (21). Although some authors considered PSV of $<25\text{cm/sec}$ is arteriogenic ED, some others considered 25-35 cm/sec is a borderline (22,23), and some others considered the arterial is considered normal when PSV $>35\text{cm/sec}$ (24).

Regarding veno-occlusive ED, the cavernous veno-occlusive function was considered normal if the RI was greater than 0.9 and the EDV was less than 5 cm/ second (24). Previous landmark study has reported that in association with a normal arterial response, an EDV $>5\text{ cm/ second}$ is accepted as the measurement at which a venous leak is present (25). Furthermore, several studies have attempted to define ultrasound parameters that are predictive of an adequate erection. It has been shown that PSV of

>30-35 cm/s is associated with normal erectile function. Additionally, the absence of venous leak, defined as EDV <5 cm/s, (26,27).

In the current study we selected the higher figure of PSV <35cm/sec to diagnose arteriogenic ED and EDV >5 cm/sec and RI <0.9 to diagnose veno-occlusive ED to better detect patients with even mild vascular impairment (arteriogenic, veno-occlusive, mixed arteriogenic-veno-occlusive) of erection.

In present study we assessed the dose needed to achieve the best response which defined as a grade 4 erection that lasted at least 15 minutes. In arteriogenic ED patients, 76% have achieved the best response. 5.3% of them with 5 µg, 63.2% with 10 µg and 31.6% with 20 µg. In veno-occlusive group 92% achieved the best response, 21.7% with 5 µg, 39.1% with 10 µg and 39.1% with 20 µg. In mixed ED patients 76% have achieved the best response however none of them have achieved the best response with 5 µg, only 10.5% with 10 µg and 89.5% have required the maximum dose of 20 µg to achieve the best response. On the other hand, in psychogenic ED group 100% achieved the best response, of them 88% needed only 5 µg and 12% need 10 µg and none of them have required 20 µg dose to achieve the best response. In line with our study, a dose-escalation study was done to investigate the efficacy and safety of PGE₁, 92.9% of ED patients have achieved an optimal response; of them 23.1% at 2.5 µg, 11.5% at 5 µg, 26.9% at 10 µg, 15.4% at 15 µg, 14.1% at 20 µg, 6.4% at 30 µg and only 2.6% at 40 µg (28). However, that study has not investigated the etiology of vascular ED and also the definition of optimal response was subjective.

A more recent study showed a significant relation between the dose of PGE₁ and the duration of erection with strongest response was in the neurogenic ED group and the lowest

response was in veno-occlusive group. Despite the correlation between this study and the current study, however that study has a relatively small number of patients and has investigated only the dose dependent response on duration without addressing the change of rigidity (9). Another study was carried out to investigate the effective dose of alprostadil assessing penile rigidity and duration of erection lasting up to 60 min however, stratification of patients in that study was not considered the exact etiology of ED (29).

Up to our knowledge, the current study is the first analysis to investigate the effect of ICI of PGE1 on rigidity and duration of erection in men with different types of vascular etiology of ED in comparison to patients with psychogenic ED. Of further clinical importance, this study has demonstrated that, the best response was achieved in patients with solely arteriogenic or veno-occlusive ED and the lowest response was obtained in patients with mixed (arteriogenic and veno-occlusive) ED. We realize that due to many exceptions, it is difficult to definitely diagnose vasculogenic ED in a clinic setting depending upon the Doppler parameters alone due to anxiety which may lead to sympathetic overriding and incomplete smooth muscle relaxation. Although these facts may render false positive results in penile Doppler tests, however, we, like others, still believe that penile Doppler is an important tool for assessment of vascular status of erection.

A potential limitation of the current study was the relatively small number of patients in each subgroup. Further, we have not used visual sexual aid which could have been enhance the Doppler result. Although, the dose-etiology relation was merely addressed, however, the innovative approach of this study to assess the dose needed to achieve the best response which defined as a grade 4 erection that lasted at least 15 minutes in patients with different types of vasculogenic ED could be of clinical significance. Further prospective randomized large-scale clinical studies are warranted to investigate the current role of ICI of vasoactive agents and

particularly PGE₁ in management of ED and to further address the impact of ICI of PGE₁ in escalating doses in patients with different types of vasculogenic ED.

Conclusion:

This study clearly has demonstrated that, patients with mixed arteriogenic and veno-occlusive ED have required the highest dose of PGE₁ to achieve the best response which defined as a grade 4 erection that lasted at least 15 minutes. Further, this study has assessed the dose needed to achieve the best response in patients with different types of vasculogenic ED that could be of clinical implication.

Conflict of Interest statement for all authors: No conflict of Interest

Funding: None

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Table (1): Frequency distribution of the studied population according to their sociodemographic and medical co-morbidity data

Variables		Group A (n= 25)	Group B (n= 25)	Group C (n= 25)	Group D (n= 25)	p value
		<i>Mean± SD</i>	<i>Mean± SD</i>	<i>Mean± SD</i>	<i>Mean± SD</i>	
Age (yrs.)		53.2±6.5	50.8±7.3	52.7±8.9	34.2±8.6	**<0.001
BMI (kg/m ²)		35.6±4.3	30.6±4.0	31.9±4.3	27.9±3.7	**<0.001
		<i>Number (%)</i>	<i>Number (%)</i>	<i>Number (%)</i>	<i>Number (%)</i>	
Residence						
Rural		2(8.0)	2(8.0)	7(28.0)	3(12.0)	*0.130
Urban		23(92.0)	23(92.0)	18(72.0)	22(88)	
Smoking						
Smoker		9(36.0)	14(56.0)	13(52.0)	10(40.0)	*0.434
None		16(64.0)	11(44.0)	12(48.0)	15(60.0)	
Medical Comorbi dity	None	10(40)	10 (40)	12 (48)	23 (92)	*<0.001
	One	10 (40)	12 (48)	7 (28)	2 (8)	
	> one	5 (20)	3 (12)	6 (24)	0 (0)	
Type of comorbid ity	DM	14 (56)	11 (44)	7 (28)	2 (8)	*0.002
	HTN	6 (24)	6 (24)	8 (32)	0 (0)	*0.029
	Other	0	1 (4)	4 (16)	0 (0)	*0.029

Abbreviations: SD: standard deviation, BMI: body mass index, DM: diabetes mellitus, HTN: hypertension

* p values are based on Chi square test. Statistical significance at p <0.05

** p values are based on One-way ANOVA test. Statistical significance at p <0.05

Table (2 a): IIEF score, ED duration, ED severity and Doppler parameters variables among the studied groups

Variables		Group A (n= 25)	Group B (n= 25)	Group C (n= 25)	Group D (n= 25)	p value
IIEF Score (Mean± SD)		15±2	14±5	11±5	20±4	**p<0.001
ED duration Median (Range) months		24 (1-60)	18 (1-48)	20 (3-36)	6 (1-24)	#p<0.001
Doppler variables (Mean± SD) cm/sec						
PSV		24.38±3.3	37.74±8.28	22.24±3.85	47.76±6.27	**p<0.001
EDV		3.96±1.02	7.68±3.1	6.22±1.6	1±0.9	**p <0.001
RI		0.83±0.08	0.71±0.65	0.79±0.05	1.33±0.3	**p 0.050
		Group A (n= 25)	Group B (n= 25)	Group C (n= 25)	Group D (n= 25)	*p value
		<i>No (%)</i>	<i>No (%)</i>	<i>No (%)</i>	<i>No (%)</i>	
ED severity	Mild	3 (12)	11(44)	9 (36)	14 (56)	*0.07
	Moder.	17 (68)	11(44)	11(44%)	8 (32)	
	Severe	5 (20) 20.0	3(12)	5 (20)	3 (12)	

Abbreviations: SD: standard deviation, ED: erectile dysfunction, IIEF: international index of erectile function, PSV: Peak systolic velocity, EDV: end diastolic velocity, RI: resistive index

* p values are based on Chi square test. Statistical significance at p <0.05

** p values are based on One-way ANOVA test. Statistical significance at p <0.05

#p-values are based on Kruskal-Wallis H test. Statistical significance at p < 0.05

Table (2 b): Pairwise comparison of ED severity, ED duration, IIEF score and doppler parameters among study groups

Groups		p value					
		*ED severity	**ED duration	*IIEF score	*PSV	*EDV	*RI
Group A	Group B	0.042	0.05	0.832	<0.001	<0.001	0.643
	Group C	0.117	0.05	0.005	0.558	<0.001	0.979
	Group D	0.007	0.002	0.001	<0.001	<0.001	0.046
Group B	Group C	0.705	0.05	0.04	<0.001	0.843	0.861
	Group D	0.659	0.002	0.001	<0.001	<0.001	0.001
Group C	Group D	0.357	0.005	0.001	<0.001	<0.001	0.016

*Analysis done by student's t test

**Analysis done by Mann-Whiteny U test $p < 0.05$ is considered statistically Significant

Table (3 a): Best response according to doses and erection duration among study groups

		Group A	Group B	Group C	Group D	*p value
N:25		NO (%)	NO (%)	NO (%)	NO (%)	
Best response	yes	19 (76)	23 (92)	19 (76)	25 (100)	0.036
	no	6 (24)	2 (8)	6 (24)	0 (0)	
Dose analysis of the best response						
Best response dose		Group A NO (%)	Group B NO (%)	Group C NO (%)	Group D NO (%)	*p value
	5 μ g	1 (5.3)	5 (21.7)	0 (0)	22 (88)	<0.001
	10 μ g	12 (63.2)	9 (39.1)	2 (10.5)	3 (12)	
	20 μ g	6 (31.6)	9 (39.1)	17 (89.5)	0 (0)	
	Total	19 (100)	23 (100)	19 (100)	25 (100)	
Duration analysis of the best response						
Erection duration		Group A Mean \pm SD	Group B Mean \pm SD	Group C Mean \pm SD	Group D Mean \pm SD	**p value
	5 μ g	14.8 (4.7)	16.2 (7.5)	11.8 (2.4)	27.6 (6.6)	<0.001
	10 μ g	25.2 (5.6)	21.8 (7.8)	18.8 (3.6)	23.3 (11.5)	<0.01
	20 μ g	27.5 (3.4)	25.8 (6.7)	22.5 (7.7)	0 (0)	0.148

Abbreviations: SD: standard deviation

* p values are based on Chi square test. Statistical significance at $p < 0.05$

** p values are based on One-way ANOVA test. Statistical significance at $p < 0.05$

Table (3 b): Pairwise comparison of erection best response among studied groups

Best Response		*p-value
Group A	Group B	<0.001
	Group C	>0.05
	Group D	<0.001
Group B	Group C	<0.001
	Group D	0.005
Group C	Group D	<0.001

* p values are based on Chi square test. Statistical significance at $p < 0.05$