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A prospective randomized study to optimize the dosage of trimix ingredients and compare its efficacy and safety with prostaglandin E_1

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Intracavernous injection of Trimix (Tx) is indicated for patients unsuitable for prostaglandin E_1 (PgE_1) injection due to lack of response, pain or cost. We believe that the ideal ratio of ingredient doses in Tx is yet to be found. We postulated that increasing the doses of individual drug components in an orderly manner would convey important data on penile hemodynamic response. Such information is needed to choose an effective and less costly alternative to PgE_1 with least side effects. We set out to evaluate the impact of varying the ingredient dosage on response and short-term safety of Tx compared with PgE_1. We prospectively randomized 180 consecutive patients with erectile dysfunction into nine equal groups and each group received a different dose of Tx, namely phentolamine (1 mg) plus one dose of PgE_1 (2.5, 5 or 10 μg) and one dose of papaverine (5, 10 or 20 mg). Each patient was injected with 20 μg PgE_1 and one dose of Tx in two clinic visits 1 week apart. Following injection, duplex ultrasound of cavernous arteries and axial rigidometry were carried out. Patients ranked the quality of erection, estimated overall satisfaction and reported time to detumescence and side effects. Patients' mean age was 50.5 ± 11.7 y with underlying organic condition in 91.1%. There were no significant differences between PgE_1 and Tx with regard to peak cavernous artery flow, time to erection, patients' satisfaction, average axial rigidity and pain. PgE_1 produced higher end diastolic velocity, shorter duration of erection and less priapism. Patients did not show a preference for either drug or any particular dosage. We conclude that even at the smallest dose of ingredients of Tx, there are no significant differences in hemodynamic effects, rigidity, pain and self-satisfaction between the two drugs. However, Tx produces a longer duration of erection and more priapism than PgE_1.
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Introduction

Intracavernous injection (ICI) remains an important therapeutic option for patients with erectile dysfunction (ED) who either do not respond to or are not suitable candidates for oral phosphodiesterase-5 (PDE-5) inhibitors.[1,2] Prostaglandin E_1 (PgE_1) is recommended as a first-line ICI treatment[3] with an optimal dose of 20 μg.[4,5] Several potentially useful combinations of three or more drugs have been used as a second-line therapy. The low doses employed for these drugs reduce the frequency of undesirable side effects and enhance their efficacy by acting synergistically. The most commonly used combination is Trimix (Tx), a mixture of papaverine, phentolamine and PgE_1. Several investigators have devised their own dose combinations (Table 1).[6–12] The real value of Tx is in salvaging those patients who respond poorly or painfully to PgE_1 alone, or need an economic yet effective treatment for ED. Standardization of the dosage and correlation of efficacy with patient response and satisfaction is lacking. We set out to evaluate, by means of an

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Table 1 Tx composition recommended by other authors

Author	*Tx stock solution*			*Ratio of ingredients*			*Injection volume (ml)*
	Papa	*PgE_1*	*Phent*	*Papa*	*PgE_1*	*Phent*	
Bennett *et al*[6]	17.6 mg/ml	5.8 μg/ml	0.58 mg/ml	30	10	1	0.25
Govier *et al*[7]	22.5 mg/ml	8.33 μg/ml	0.83 mg/ml	27	10	1	0.36
Israilov *et al*[12]	19.4 mg[a]	16.4[a]	1.6[a]	12.1	10.25	1	NA
Marshall *et al*[8]	12 mg	9 μg	1 mg	12	9	1	0.1–0.8
Shenfield *et al*[9]	4.5 mg/0.5 ml	5 μg/0.5 ml	0.25 mg/0.5 ml	18	20	1	0.5
Mulhall *et al*[10]	30 mg	10 μg	1 mg	30	10	1	NA
	30 mg	25 μg	2 mg	15	12.5	1	NA
Montorsi *et al*[11]	150 mg	30 μg	5 mg	30	6	1	0.18–0.21
	300 mg	100 μg	10 mg	30	10	1	0.18–0.21
	300 mg	200 μg	20 mg	15	10	1	0.18–0.21

Papa = papaverine; Phent = phentolamine; NA = not specified.
[a]mean dose.

acute, prospective, randomized, single blind study, the various dose combinations of Tx *versus* PgE_1 20 μg using both subjective and objective end points.

Hypothesis: We think that the ideal ratio of ingredient doses in Tx is yet to be found. The effect of increasing individual drug components on penile response is not known. Such information is needed to choose an effective and less costly alternative to PgE_1 with least side effects.

Patients and methods

A total of 180 men complaining of ED and presenting sequentially to the Urology Outpatient Department, from July 2000 to December 2002 were prospectively randomized to nine study groups (T1–T9). All patients with ED for at least 6 months were eligible except patients with a history of priapism, sickle cell anemia or previous surgical treatment for ED. Each group of patients received one dose of Tx or 20 μg PgE_1 at a clinic visit and 1 week later received the alternative drug. The order of injection was randomized and the patients were blinded to the drugs and doses injected. In this design, each patient served as his own control. Data were collected at the end of the first visit and at the beginning and end of the second visit. At a third visit, further management was discussed.

Each patient underwent relevant history taking, physical examination and a focused neurological examination. Patients were assessed for psychological risk factors (insomnia, anorexia, depression, marital problems, anger, stress, decreased libido and unaccepted performance). Starting with the 23rd patient, the five-item version of the International Index of erectile function-5 (IIEF-5) was used.[13] Random blood sugar, serum cholesterol and serum triglycerides were determined for all patients. Serum prolactin and serum testosterone were determined if the patient had decreased libido.

Table 2 Drug doses and cost in Egyptian pounds

Tx no	*PgE_1 (μg)*	*Papaverine (mg)*	*Phentolamine (mg)*	*Cost*
Tx 1	2.5	5	1	3.25
Tx 2	2.5	10	1	3.5
Tx 3	2.5	20	1	3.75
Tx 4	5	5	1	5
Tx 5	5	10	1	5.25
Tx 6	5	20	1	5.5
Tx 7	10	5	1	9.5
Tx 8	10	10	1	9.75
Tx 9	10	20	1	10
PgE_1	20	—	—	18

Pharmacologic duplex ultrasound examination of the penis was carried out in a quite private room. Drug injection into the left lateral side of the penis was followed by 1 min of local pressure and 5 min of manual self-stimulation. The composition of drugs used and their cost is shown in Table 2. Under sterile conditions, saline was used to constitute the doses from the following drugs: prostin VR 1 ml/500 μg (Alprostadil, Pharmacia & Upjohn, USA), papaverine (Vasorin, 1 ml/30 mg papaverine HCl, Memphis Co., Cairo, Egypt) and phentolamine (Regitine, 1 ml/10 mg, Novartis Pharma AG, Basel, Switzerland). The stock solution was refrigerated at 4°C in a glass container. The solution was discarded if not consumed within 30 days.

The following information was recorded: blood pressure 5 min after injection, the time taken to complete erection, the examiner's grading of erection[14] and the patient's self-grading of erection compared with erections at home. Complications at the site of injection, degree of pain, patient's satisfaction of erection (%), preference for one drug and time taken to complete detumescence were recorded at the second visit. The Sonoline Sienna Ultrasound Imaging System and a scanner probe 7.5–10 Hz (Siemens Medical System, Inc., Ultrasound Group, Germany) were used. The penis was

scanned at the penoscrotal junction from the lateral aspect. The diameters of cavernosal arteries, peak systolic velocity (PSV) and end diastolic velocity (EDV) were measured and the resistive index (RI) calculated. The Doppler angle was manually adjusted to get the best flow. Rigidometry was carried out to evaluate the minimal axial pressure to bend the erect penis, using the Digital Inflection Rigidometery (RID 101C, Uroan XXI Sl., Electromedicina, Palma Mallorca, Baleares, Spain). The cup of the transducer was applied slowly to the glans in the axis of the erect shaft. Three consecutive readings of the actual axial (buckling) rigidity were averaged.

In all cases, the same physician conducted the assessment of the patient in both sessions.

Analysis of data

We analyzed the results of history and physical examination, laboratory tests and duplex US to characterize the etiological factors in our patient population using methods previously published.[15] Patients were considered to have an organic etiology if they had a concurrent disease known to cause ED, had surgery or trauma known to cause ED, had abnormal physical examination denoting vascular or neurological disease or had abnormal laboratory tests known to be associated with ED. The rest of the patients were evaluated for abnormal cavernosal artery flow; patients with PSV $\leq$ 25 cm/s unilateral or bilateral were labeled as having arteriogenic ED. The remaining patients were evaluated for abnormal venous flow indirectly using the EDV and RI data. Those patient with EDV $>$ 5 cm/s or RI $\leq$ 0.9 unilateral or bilateral were considered to have venogenic ED. The remaining patients having negative clinical and testing evaluation were considered to have pure psychogenic ED. Patients who had organic ED and psychogenic risk factors were considered to have combined etiology.

The response data of all Tx and PgE_1 doses were pooled. Each group of data (one Tx dose *versus* PgE_1) was evaluated regardless of the order of administration using SPSS version 10 software. Descriptive statistics, ANOVA and two-tailed *t* test for continuous data, frequency tables, crosstabulation and chi-square for categorical data were applied.

Results

From the 180 patients, one in group T9 was withdrawn because he developed priapism during the first visit and did not complete the study. He was included only for the analysis of priapism.

Patient demographics at baseline

The mean age of the study population was 50.5 y (s.d. 11.7). A total of 160 patients (89.4%) were currently married. They suffered ED for 40.2 months (s.d. 42.7). The degree of ED as indicated by the IIEF-5 questionnaire score in 158 patients was 7.6 (s.d. 5.8). Thirty six patients (20%) reported that they had complete ED, 137 (76.5%) patients reported weak erection and six patients (3.4%) reported difficulty to maintain erection. All the above baseline factors were not statistically significantly different among the nine Tx treatment groups.

Etiology of ED (Table 3)

We had 137 (76.5%) patients with organic disease underlying their ED. Of the remaining patients, 20 (11.2%) had arterial disease on duplex US of the cavernous arteries and additional six patients (3.4%) had pure venous leakage. The remaining 16 patients (8.9%) were considered to have psychogenic etiology with no evidence of any organic disease. The total number of patients with organic lesions adds up to 163 (91.1%); of those patients, 67 (37.4%) had combined psychogenic risk factors. No significant differences were found among the nine Tx treatment groups for organic, psychogenic and combined etiologies (Pearson chi-square, $P = 0.92$). Hormones were determined in seven out of 11

Table 3 Etiology of ED ($N = 179$), more than one medical condition could coexist

	N *(%)*
Recreation drug user	12 (6.7)
Cardiovascular disease	85 (47.5)
Hypertension	47 (26.2)
Coronary or heart disease	14 (7.8)
Hypercholesterolemia	27 (15.1)
Hyperlipidemia	36 (20.1)
Urinary tract pathology	19 (10.6)
Penile nodules	7 (3.9)
Urinary tract infection	4 (2.2)
Atrophic or absent testes	6 (3.4)
Cancer prostate	2 (1.1)
Diabetes mellitus	56 (31.3)
Neurological disease	23 (12.8)
Major pelvic surgery	9 (5)
Spinal cord injury or surgery	6 (3.4)
Epilepsy	3 (1.7)
Miscellaneous	5 (2.8)
Endocrine gland disease	6 (3.4)
Hypogonadism	3 (1.7)
Hyperprolactinemia	3 (1.7)

patients with decreased libido. Serum prolactin was high in three patients (23–68 mg/dl), and total serum testosterone was low in three patients (0.1–2.8 ng/dl). Patients with hypertension had a mean systolic blood pressure (SBP) of 161 ± 12 mmHg and a mean diastolic blood pressure (DBP) of 101 ± 6 mmHg.

Analysis for the results of injection for all patients (n = 179)

No patient developed a hematoma at the injection site. In response to injection, the diameter of cavernosal arteries significantly increased (Table 4). There was a significant difference between the effect of drugs on EDV and the duration of erection. A longer duration of erection and less EDV was noted with Tx compared with PgE_1 (Table 5). No differences were found in the hemodynamics and quality of erection, satisfaction and pain (Tables 5 and 6). There was a significant incidence of priapism with Tx (Tables 6 and 7). Only one patient developed

Table 4 Cavernous artery diameter before and 5 min after injection (*N* = 179)

	Before (mm)	*s.d.*	*After (mm)*	*s.d.*	P
PgE_1					
Rt	0.53	0.12	0.89	0.21	<0.001
Lt	0.51	0.11	0.86	0.21	<0.001
Tx					
Rt	0.51	0.13	0.92	0.21	<0.001
Lt	0.51	0.12	0.89	0.20	<0.001

Table 6 Comparison of categorical data after intracavernous injection of PgE_1 and Tx, (crosstabulation and Pearson chi-square)

	PgE_1	*Tx*	P
Degree of erection, N (%)			
G1	6 (3.4)	8 (4.5)	*0.693*
G2	10 (5.6)	15 (8.4)	
G3	41 (22.9)	36 (20.1)	
G4	61 (34.1)	54 (30.2)	
G5	61 (34.1)	66 (36.9)	
Satisfaction, N (%)			
Good	78 (43.6)	80 (44.7)	*0.728*
Moderate	60 (33.5)	51 (28.5)	
Minimal	24 (13.4)	28 (15.6)	
None	17 (9.5)	20 (11.2)	
Self-grading of erection compared with home, N (%)			
Worse	13 (7.3)	13 (7.3)	*0.852*
Same	14 (7.8)	17 (9.5)	
Better	152 (84.9)	149 (83.2)	
Degree of axial rigidity, N (%)			
Rigid (>999 gm)	62 (34.6)	65 (36.3)	*0.92*
Moderate (500–999 gm)	59 (33)	53 (29.6)	
Mild (1–499 gm)	42 (23.5)	45 (25.1)	
None (0 gm)	16 (8.9)	16 (8.9)	
Degree of pain, N (%)			
None	147 (82.1)	153 (85.5)	*0.81*
Mild	15 (8.4)	13 (7.3)	
Moderate	14 (7.8)	9 (5)	
Severe	3 (1.7)	4 (2.2)	
Priapism, N (%)			
Yes	1 (0.6)	9 (5)	*0.022*
No	179 (99.4)	170 (94.4)	
Not done		1 (0.6)	

Table 5 Hemodynamic effects of PgE_1 and Tx doses (*N* = 179)

	PgE_1	*Tx*	P
PSV (cm/s ± s.d.)			
Rt	30.12 ± 12.17	29.06 ± 12.48	0.33
Lt	29.69 ± 12.45	28.58 ± 12.20	0.27
Cavernous artery diameter after injection (mm ± s.d.)			
Rt	0.89 ± 0.21	0.92 ± 0.21	0.05
Lt	0.86 ± 0.21	0.89 ± 0.2	0.07
Lt EDV (cm/s ± s.d.)			
Rt	4.2 ± 3.8	3.5 ± 3.1	<0.01
Lt	4.4 ± 4.1	3.3 ± 2.9	<0.001
Degree of erection (1–5 ± s.d.)	3.90 ± 1.04	3.87 ± 1.14	0.5
Time to erection (min ± s.d.)	10.40 ± 5.51	10.70 ± 5.52	0.29
Duration of erection (min ± s.d.)	92.6 ± 66.7	120.4 ± 91.2	<0.001
Satisfaction (% ± s.d.)	64.36 ± 26.21	63.41 ± 28.06	0.48
Systolic BP at 5 min (mmHg ± s.d.)	125.47 ± 19.64	125.50 ± 18.28	0.98
Diastolic BP at 5 min (mmHg ± s.d.)	82.18 ± 11.12	81.34 ± 11.06	0.27
Average axial rigidity (gm ± s.d.)	825.91 ± 519.95	835.11 ± 552.37	0.66

Table 7 Priapism and pain, crosstabulation and chi-square analysis

		Priapism			*Pain*				
Group		*No*	*Yes*	P	*None*	*Mild*	*Moderate*	*Severe*	P
T1	PgE_1	20		0.147	17	1	2		0.348
	Tx	18	2		19	1			
T2	PgE_1	20			18	1	1		0.513
	Tx	20			18	2			
T3	PgE_1	20		0.311	16	2	1	1	0.881
	Tx	19	1		16	1	2	1	
T4	PgE_1	20			15	2	2	1	0.283
	Tx	20			19		1		
T5	PgE_1	20		0.147	19	1			1
	Tx	18	2		19	1			
T6	PgE_1	20		0.147	14	4	2		0.601
	Tx	18	2		14	2	3	1	
T7	PgE_1	20		0.147	19		1		0.55
	Tx	18	2		17	1	1	1	
T8	PgE_1	20			14	4	1	1	0.735
	Tx	20			16	3	1		
T9	PgE_1	19	1	0.323	16	1	2	1	0.637
	Tx	19			15	2	1		
All	PgE1	179	1	0.022	148	16	12	3	0.81
	Tx	170	9		153	13	9	4	

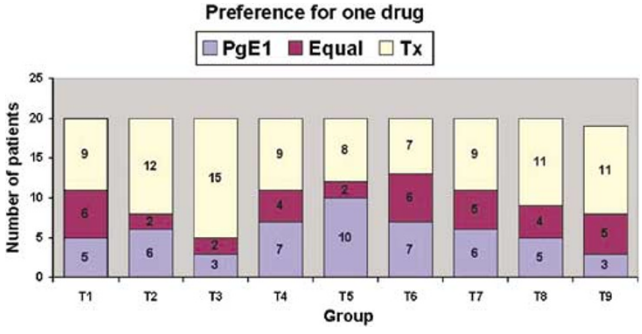

Figure 1 Patients' preference for one drug within each group (crosstabulation and Pearson chi-square asymp. sig., two-sided, $P = 0.413$).

priapism after the injection of PgE_1; he failed to respond to pharmacological reversal and was successfully treated with a cavernospongiosal shunt.

Patients' preference for one drug

In total, 52 patients (29.1%) stated that PgE_1 gave a better response and 91 patients (51.4%) reported greater satisfaction with Tx. Only 36 patients (20.1%) stated that both drugs gave a similar response. These differences were not statistically significant (Figure 1).

Analysis for the results of injection for patients within each group (n = 20): continuous data (Table 8)

All parameters were not significantly different except that PgE_1 had a shorter duration to erection in group 1 and Tx had a lower Lt-EDV in groups 2, 6 and 9 and longer duration of erection in groups 1, 3 and 7.

Categorical data

There was no significant difference between Tx and PgE_1 with regard to degree of erection, grade of satisfaction, self-grading of erection compared with erections at home, degree of rigidity, pain and priapism within any group, using crosstabulation and chi-square analysis. Table 7 shows the distribution of priapism and pain among groups. Although

Table 8 Comparison between hemodynamic effects and satisfaction within each group

	PSV cm/sec (s.d.)		*EDV cm/s (s.d.)*		*Satisfaction % (s.d.)*	*Duration to erection min (s.d.)*	*Average axial rigidity g (s.d.)*
	Rt	*Lt*	*Rt*	*Lt*			
PgE_1	33 (15)	29 (11)	6 (5)	6 (4)	64.5 (29.7)	**83.4 (68.7)**	682.05 (538.7)
T1	33 (18)	31 (17)	5 (3)	5 (3)	60.5 (30.3)	**115.5 (111.5)**	671.05 (530.4)
P	0.993	0.701	0.083	0.129	0.383	**0.03**	0.862
PgE_1	34 (13)	34 (14)	6 (4)	**7 (5)**	53.5 (27)	65.25 (45.8)	586.7 (469.3)
T2	28 (12)	30 (14)	5 (4)	**4 (3)**	48 (24.8)	74.75 (58)	584.2 (458.2)
P	0.152	0.175	0.245	**0.011**	0.261	0.354	0.972
PgE_1	30 (10)	30 (12)	3 (4)	3 (4)	73.5 (18.8)	**80.5 (43.9)**	1054.7 (499.9)
T3	27 (11)	26 (21)	2 (2)	2 (2)	75.5 (19.9)	**118.75 (80.6)**	1057.85 (550.5)
P	0.482	0.854	0.899	0.153	0.173	**0.015**	0.547
PgE_1	27 (12)	27 (14)	4 (3)	4 (3)	61.5 (29.56)	**77.75 (56.95)**	654.55 (399.53)
T4	26 (11)	28 (11)	4 (4)	4 (3)	56.5 (32.29)	**117.75 (83.25)**	685.3 (475.9)
P	0.597	0.577	0.591	0.916	0.178	**0.06**	0.586
PgE_1	30 (9)	28 (13)	5 (4)	5 (5)	64.75 (24.95)	116.75 (93.83)	880.5 (514.16)
T5	28 (12)	27 (12)	4 (3)	4 (3)	62.5 (28.49)	137.5 (124.26)	883.85 (575.01)
P	0.283	0.911	0.422	0.186	0.508	0.454	0.965
PgE_1	28 (14)	29 (13)	3 (2)	**4 (2)**	58.5 (31.29)	91.5 (67.65)	821.9 (597.27)
T6	31 (12)	26 (12)	6 (14)	**3 (2)**	60.25 (32.71)	104.75 (98.07)	911.1 (631.59)
P	0.251	0.286	0.369	**0.046**	0.577	0.469	0.161
PgE_1	28 (12)	28 (10)	2 (2)	3 (4)	69.5 (28.92)	**116.75 (75.4)**	1048.85 (529.72)
T7	25 (10)	29 (11)	2 (2)	2 (3)	73.5 (29.65)	**152.5 (82.02)**	1013.05 (585.84)
P	0.482	0.854	0.899	0.153	0.173	**0.015**	0.547
PgE_1	29 (14)	30 (13)	4 (3)	5 (5)	63.75 (23.11)	**98.75 (63.97)**	734.55 (467.9)
T8	32 (12)	27 (10)	3 (2)	4 (3)	61 (24.42)	**142.65 (94.43)**	681.75 (470.56)
P	0.294	0.138	0.419	0.231	0.447	**0.011**	0.454
PgE_1	32 (9)	32 (12)	3 (3)	**4 (3)**	70 (18.03)	103.42 (63.84)	976.95 (500.36)
T9	32 (12)	33 (13)	3 (3)	**3 (3)**	73.42 (19.37)	119.47 (61.66)	1038 (529.1)
P	0.918	0.716	0.084	**0.031**	0.235	0.129	0.329

The bold values show statistically significant differences between groups.

globally Tx is associated significantly with priapism, within each group this difference is less prominent. PgE_1 is known to cause pain, but in our study it was found to be no more painful than Tx. There was a trend towards preference for Tx but the overall difference was not statistically significant (Figure 1).

Discussion

In spite of oral drug therapy for ED, there is a considerable number of candidates for self-injection therapy. These include patients who do not respond to or have a contraindication for PDE-5 inhibitor treatment. In addition, some patients prefer the rigidity provided by injections. In patients undergoing ICI therapy and given the option to try sildenafil, 36.2% decided to use injections most of the time or at least sporadically.[2] The association of multiple vasoactive drugs produces a full erectile response in more than 90% of patients.[6] In non-responders to doses as high as 40 μg PGE_1, Tx combination produced a response in 31%.[16] The cost of the medication is another important issue where Tx has an advantage (Table 2). In men on ICI therapy, the total dropout rate was 31% and 28.3% dropped out because the therapy was too expensive.[10]

A total of 163 patients (91.1%) had an organic condition that could affect their erection. This figure is consistent with the patients' characteristics of office-based studies of ED.[15] We evaluated a PgE_1 dose of 20 μg because many authors agree that most ED patients attain maximal hemodynamic and erectile response at this dose.[4,5] The end point of ED treatment is to attain and maintain penile rigidity sufficient for sexual intercourse. We defined these end points in a subjective and objective manner. Of our patients, 93% reported that erection attained in the office is the same or better than what they get at home during sexual activity (Table 6). This indicates that the negative impact of the stress

of testing environment on the pharmacological response was minimal. Axial rigidity (penile buckling force) is the physical parameter which best defines objectively the capability of the erect penis to resist deformation during vaginal intromission and continued pelvic thrusting following penetration.[17] Penile axial rigidity >500 g is considered sufficient to penetrate a well-lubricated woman. The average rigidity attained by our patients in both groups was above 800 g. Overall, 67% of the study group attained a penile axial rigidity sufficient for penetration (Table 6). No difference in rigidity could be demonstrated in pooled data of Tx *versus* PgE_1 or between any individual dose of Tx or PgE_1. This is particularly important for the smallest dose of Tx which in terms of rigidity fares equal to 20 μg of PgE_1. These results were consistent with other rigidity end points determined subjectively by the examining physician or assessed by the patient himself. In our study, there was no significant difference in the latency time between the different doses of Tx and PgE_1. It is not surprising that the smaller doses of Tx produce their effect as fast as the high dose of PgE_1 because of the multiplicity of the levels of action Tx targets in cavernous tissue. In contrast, the duration of erection was significantly longer after Tx ($\sim$120 min) even though PgE_1 in our study produced longer periods of erection ($\sim$90 min) than those reported by others ($\sim$50 min).[18] The hemodynamic responses of the different drugs were compared to highlight subtle changes that may not culminate in a usable erection and yet are significant. The average value of PSV of our patients falls below the normal value.[19] This indicates that most of our patients have a vascular etiologic factor to a mild degree. There was no significant difference in PSV response between Tx and PgE_1 in any of the tested doses. There was a distinct advantage of Tx over PgE_1 with regard to the effect on venous flow. Tx produced more reduction in EDV. This effect might be beneficial in cases with cavernovenous leakage. The mechanism by which Tx more selectively reduces cavernovenous resistance is not known; it might be attributable to more complete relaxation of the cavernous sinuses by Tx than PgE_1 or the multiplicity of target sites and mechanisms of action of the multiple Tx ingredients. This difference may explain why Tx is more effective than PgE_1 and salvages 30% of nonresponders.[16]

The incidence of priapism after PgE_1 in our series is similar to that reported worldwide (0.36%).[20] The incidence of priapism for Tx varies between 0 and 3.7%.[7,12,21] This variability in incidence is expected because of the different doses of papaverine used and different definitions for priapism. With Tx, our study showed that the overall incidence of priapism is 5%, which is significantly higher than PgE_1. We had more priapism than what was reported for Tx probably because we used Tx in a nonflexible dose, did not titrate for best response and did not select nonresponders to other regimens of injections to receive Tx. It is noteworthy that in individual groups of 20, however, the difference was not statistically apparent. Pain is quite common with PgE_1 alone; it has been noted in 7.2% in a worldwide survey with a range of up to 52%.[20] The overall occurrence of pain in our series for PgE_1 (17.9%) is consistent with previous reports. Tx was associated with a high incidence of pain (14.5%). This is in contrast to the reported incidence of pain in some studies (3.5%)[7] and on the other hand is comparable with or even lower than others (12.5–34.4%).[6,12] A probable explanation for the high incidence of pain in our study is that apprehension of the needle aggravates pain. As the process of titration and home injection is continued, the patient's fears decrease and the actual pain related to the drug and not to the injection becomes apparent. Our patients had no complications at the site of injection, which is probably related to the small number of injections and to the performance of the injection by the physician. In our study, patients tended to prefer Tx in spite of the fact that no difference was observed in subjective perception of rigidity or side effects. These results indicate that patients' preferences could not be interpreted with a single parameter, such as rigidity, onset of erection, duration, pain, priapism etc.; however, the interplay of these factors combined may be detrimental to patient's preference.

The choice of Tx ingredients has been at best arbitrary and not based on scientific evidence. Our study demonstrates in an objective way a logical approach to the use of Tx. The efficacy of Tx and PgE_1 is comparable with respect to erection and hemodynamic effects. Only the duration was longer for Tx. These results indicate that the smallest dose of Tx can replace PgE_1 from an efficacy point of view. Factors that may affect the choice of treatment may include availability of the drug, price, patient's preference and the etiology of ED. In the USA, PgE_1 is the only approved drug for ICI; Tx, however, is used as a salvage medication in nonresponders. Of particular interest is that Tx might be more specific in stimulating the veno-occlusive mechanism than PgE_1. In conclusion, we believe that this study has provided data that will assist the physician in choosing the ICI drug regimen that is most suitable to his ED patient. Particularly, the smallest doses of Tx ingredients are as effective as PgE_1 20 μg at a fraction of the cost.

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