



Combined intracavernous vasoactive drugs and sildenafil citrate in treatment of severe erectile dysfunction not responding to on-demand monotherapy

Ahmed M. Al-Adl, Osama Abdel-Wahab, Tarek El-Karamany & Ashraf A. Aal

To cite this article: Ahmed M. Al-Adl, Osama Abdel-Wahab, Tarek El-Karamany & Ashraf A. Aal (2011) Combined intracavernous vasoactive drugs and sildenafil citrate in treatment of severe erectile dysfunction not responding to on-demand monotherapy, Arab Journal of Urology, 9:2, 153-158, DOI: [10.1016/j.aju.2011.06.008](https://doi.org/10.1016/j.aju.2011.06.008)

To link to this article: <https://doi.org/10.1016/j.aju.2011.06.008>



© 2011 Arab Association of Urology



Published online: 05 Apr 2019.



Submit your article to this journal [↗](#)



Article views: 1967



View related articles [↗](#)



Arab Journal of Urology
(Official Journal of the Arab Association of Urology)

www.sciencedirect.com



ANDROLOGY/SEXUAL MEDICINE

ORIGINAL ARTICLE

Combined intracavernous vasoactive drugs and sildenafil citrate in treatment of severe erectile dysfunction not responding to on-demand monotherapy

Ahmed M. Al-Adl *, Osama Abdel-Wahab, Tarek El-Karamany, Ashraf A. Aal

Urology Department, Benha Faculty of Medicine, Egypt

Received 31 May 2011, Accepted 27 June 2011

Available online 15 September 2011

KEYWORDS

Erectile dysfunction;
Therapy;
Intracavernous;
PGE1;
PDE-5I

ABBREVIATIONS

ED, erectile dysfunction;
CDUS, colour Doppler
ultrasonography; PGE1,
prostaglandin E1; EH(S),
Erection Hardness (Score);
ICI, intracavernous injection;
PSV, peak systolic
velocity; EDV, end-diastolic
velocity; RI, resistance index;
PDE, phosphodiesterase;
NO, nitric oxide; SHIM,
Sexual Health Inventory for
Men; VOD, veno-occlusive
dysfunction; EDITS, Erectile
Dysfunction Inventory of
Treatment Satisfaction

Abstract Objective: To investigate the effect of chronic use of sildenafil and intracavernous injection (ICI) with trimix in men not responding to on-demand monotherapy with sildenafil or ICI with prostaglandin-E1 (PGE1).

Patients and methods: The study included 40 patients with erectile dysfunction (ED), with a mean (SD) age of 50.7 (11.3) years and unresponsive to on-demand sildenafil or ICI with PGE1 as monotherapy. They were assessed using the Sexual Health in Men (SHIM)-5 score for ED severity, penile colour Doppler ultrasonography (CDUS) for peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistance index (RI) with an ICI test using 0.25 mL of trimix of papaverine, PGE1 and phentolamine. Testosterone, prolactin and cholesterol levels were assessed. Patients received 25 mg sildenafil daily for 8 weeks, combined with twice weekly ICI with 0.25 mL of trimix. After treatment, the Erection Hardness Score (EHS), penile CDUS with ICI and ED Inventory of Treatment Satisfaction were assessed.

Results: The mean (SD) SHIM-5 score before treatment was 8.3 (0.5) in 15 of the 40 men and 6.3 (0.4) in 25. Penile haemodynamics were normal in five (13%), showed arterial insufficiency in five (13%), venous occlusive disease in 26 (65%) and mixed vascular in four (10%). There was an improved SHIM-5 score in 28 (70%) patients, as shown by their haemodynamic values, duration of erection and EHS with therapy, and 66% satisfaction with treatment. Adverse effects (penile pain, headache, facial flushing, dyspepsia, nasal congestion, dizziness) were reported in 17 patients (43%).

Conclusion: Chronic use of trimix plus daily low-dose sildenafil improved penile haemodynamics in these patients with ED not responding to on-demand phosphodiesterase-5 inhibitors or ICI with PGE1 monotherapy.

© 2011 Arab Association of Urology. Production and hosting by Elsevier B.V. All rights reserved.

* Corresponding author. Tel.: +20 133237560, +20 105205964, 966533315415 (mobile); fax: +20 96627380032.

E-mail addresses: ameladl@hotmail.com, ahmed_eladl2002@yahoo.com (A.M. Al-Adl).



Introduction

The definition of erectile dysfunction (ED) is the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [1]. ED reduces sexual satisfaction and affects partner relationships [2]. A treatment goal should focus on restoring full sexual functioning, not only improving erection [3]. Erection hardness (EH) is a fundamental component of erectile function [4] and could best define the response to treatment for ED, and can be considered a suitable assessment [5]. Phosphodiesterase type 5 (PDE-5) inhibitors maintain an erection by inhibiting the catabolism of cGMP, hence facilitating erection after oral intake, with sexual stimulation required to activate the nitric oxide (NO)-cGMP pathway [6]. In practice, some patients had no or a suboptimal response to PDE-5 inhibitors, and to intracavernous injection (ICI) of prostaglandin (PG) E1. McMahon et al. [7] used the combined therapy of sildenafil plus ICI with triple agents as salvage therapy for these patients; they used sildenafil up to 100 mg at 1 h before and triple-agent ICI 10 min before planned sexual intercourse. Park et al. [8] evaluated the clinical response and the haemodynamic changes in the cavernous arteries, and found that combined oral sildenafil and ICI with trimix (papaverine, PGE1 and phentolamine) is the best combination for a pharmacological erection test [8].

Combined therapy with a PDE-5 inhibitor and a second agent that targets another vascular, endocrine or neuronal pathway might provide a possible treatment for patients with a suboptimal response to ICI with PGE1, or those not responding to on-demand PDE-5 inhibitors. Our treatment goal was based on satisfaction with the quality of erection, by assessing the efficacy of combined chronic therapy with daily low-dose sildenafil citrate and the booster effect of ICI with trimix twice weekly in this selected group of patients with ED.

Patients and methods

The study included 23 patients with ED who did not respond to PDE-5 inhibitors, and 17 dissatisfied with their EH after ICI with PGE1, who presented to our sexual dysfunction clinic, referred by other physicians or presented for further evaluation during the period from May 2008 to August 2010. Inclusion criteria comprised patients with ED for ≥ 6 months and not responding to previous treatment with PDE-5 inhibitors at maximum dose and ICI with PGE1. Exclusion criteria included hypertension (blood pressure $< 90/50$ mmHg) or uncontrolled hypertension (blood pressure $> 170/110$ mmHg); clinically significant cardiovascular disease in the last 3 months; current or anticipated use of nitrates or NO donors, and known hypersensitivity to or previous severe side-effects from sildenafil. Patients with poor manual dexterity, poor visual acuity, morbid obesity, serious psychiatric and patients with Peyronie's disease or idiopathic priapism were excluded from study.

After a complete history and a physical examination, informed consent for participation was obtained from all patients, and possible risks explained thoroughly according to the Declaration of Helsinki. The option to participate or to abstain from participation was given to the patients; in all, 40 patients agreed to participate in this study.

To evaluate their baseline ED, the Sexual Health Inventory for Men (SHIM-5) questionnaire was used at the baseline visit and after 2 months, with threshold scores set as no ED > 22 ,

mild 17–21, moderate 8–16, and severe ED < 7 [9,10]. The questions were preceded by 'over the past 4 weeks' and not 'over the past 6 months' as in the original version. Laboratory tests included serum testosterone, blood glucose and total cholesterol levels, and a complete blood count.

The penile haemodynamics of pharmacologically induced erection in all patients with ED was evaluated with colour Doppler ultrasonography (CDUS), using a Model SSA-350 A system (Toshiba Inc., Tokyo, Japan) at the beginning and repeated after 8 weeks, with measurements of the peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistance index (RI), calculated as $(PSV-EDV)/PSV$, from the both cavernosal arteries before and after ICI with 0.25 mL of trimix solution (1 mL of the solution contained 18.7 mg papaverine, 6.25 μ g PGE1 and 0.62 mg phentolamine) [11]. Readings were registered from the best artery at any time for analysis starting 2–3 min after ICI. Priapism after trimix injection was considered an exclusion criterion from the study.

Patients with a normal PSV (≥ 30 cm/s) and normal EDV (≥ 5 cm/s) were classified as having a normal penile blood flow study. ED caused by arterial insufficiency was defined as a PSV of < 30 cm/s with normal EDV (≥ 5 cm/s). The diagnosis of veno-occlusive dysfunction (VOD) was defined as a normal PSV (≥ 30 cm/s) with an abnormal EDV (> 5 cm/s). Patients who could not be classified into the above categories were defined as having mixed-type ED [12,13]. If there was a successful response after ICI in the clinic, the patient was taught the technique of self-injection and supplied with drugs for home use, but those who had subsequently failed to attend follow-up appointments were excluded. Any other treatments for ED were to be terminated before the study and after a 2-week wash-out patients received 25 mg sildenafil citrate (ViagraTM, Pfizer, NY, USA) to be taken not more than once daily for 8 weeks, and ICI with 0.25 mL trimix to be used twice per week.

The following drugs were used to constitute the stock solution: Vasorine (each 1 mL containing 30 mg papaverine HCl, Memphis Co., Cairo, Egypt), prostin VR 1 mL containing 500 μ g PGE1, (Alprostadil, Pharmacia & Upjohn, USA) and Regitine (1 mL containing 10 mg phentolamine, Novartis Pharma AG, Basel, Switzerland). The ratio of ingredients was 30 mg papaverine: 10 μ g PGE1:1 mg phentolamine [11]. Normal saline was used to constitute the doses and the solution was kept at 4 °C in a glass container (discarded if not consumed within 30 days).

Patients were instructed to attempt sexual activity at least twice each week and to complete an event-log worksheet, and to document compliance the event logs were compared with unused study medication.

EH was evaluated subjectively using the EH Score (EHS), a 5-point response score denoting how the patient would rate his erection, with scores of 0 (penis does not enlarge), 1 (penis is larger but not hard), 2 (penis is hard but not hard enough for penetration), 3 (penis is hard enough for penetration but not completely hard) and 4 (penis is completely hard and fully rigid) [4]. At visit 2 (month 2), satisfaction was assessed with the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) [14], using the patient version of the EDITS, which includes 11 questions, each scored on a 0–4-point scale, with a higher score indicating greater satisfaction. The mean score of all 11 questions is multiplied by 25 to obtain the EDITS index, resulting in a treatment satisfaction ranging from 0 (lowest satisfaction) to 100 (highest satisfaction). The scores define

four levels of satisfaction (i.e. 0–24, not satisfied; 25–49, dissatisfied; 50–74, satisfied; and 75–100, very satisfied). EDITS scores of >50 indicate satisfaction with treatment [14]. An Arabic translation of the questionnaires (SHIM-5, the EHS and EDITS) was adopted using the back-translated technique [15] ensuring a functionally equivalent translation and better understanding of responses to the original versions.

The data were analysed using standard statistical methods, with a one-way anova used to detect variance in variables of vascular diagnosis, and the Dunnett *t* (two-sided) post hoc test used to detect differences between patients with arterial insufficiency, VOD and mixed disease vs. normal responders. The Kruskal–Wallis test was used to detect differences between groups in the rigidity response grade 3 and 4. Student’s *t*-test for paired and unpaired samples was used as appropriate. For all tests, *P* < 0.05 was considered to indicate statistical significance and all statistical tests were two-sided.

Results

In all, 40 patients completed the course of combined treatment and were evaluated. The mean (SD, range) age was 50.7 (11.3, 35–72) years and the pretreatment SHIM-5 score was 7.4 (0.8, 6–9), with 15 patients (38%) with moderate ED and 25 (63%) with severe ED. The duration of ED (under the previous therapies with maximum dosing of PDE-5 inhibitors and ICI of PGE1) was 16.8 (8.8, 6–36) months. For concomitant conditions, of the 40 patients 21 (53%) had no comorbid disease, nine (23%) had diabetes mellitus, three (8%) had diabetes and hypertension, and seven (18%) had undergone prostatectomy.

Laboratory results showed a mean (SD), range total testosterone level of 12.5 (3.5, 7.9–19.4) nmol/L (normal range 9.9–

27.8), prolactin of 9.9 (1.9, 6.4–15.3) ng/mL (normal range 4.04–15.2) and total cholesterol of 175.7 (13.5, 150–200) mg/dL (normal range < 200 mg/dL).

For the vascular diagnosis, pretreatment haemodynamic variables showed a normal response in five (13%) men, arterial insufficiency in five (13%), VOD in 26 (65%) and mixed arterial and VOD in four (10%) (Table 1). The rigidity grade was 3 or 4 in all those with a normal vascular response, two of five with arterial insufficiency, and 10 of 26 with VOD (39%). None of those with mixed vascular aetiology had a positive rigidity response of grade 3 or 4. After the combined treatment, the haemodynamic findings of the 40 patients showed an improvement in 28 (70%); their mean (SD, range) age was 46.1 (8.9, 35–65) years.

Comparing variables before and after treatment in the 28 responders, there was a significant improvement in haemodynamic values, SHIM-5 score, time to and duration of erection, and EHS (Table 2).

Table 3 shows the comparison between responders and non-responders, where there was a significant difference in age, duration of ED, SHIM-5 score before and after treatment, time to and duration of erection, EHS with treatment, and mean and standardised EDITS.

The 12 non-responders included two of five with arterial insufficiency, nine of the 26 with VOD (35%) and one of the four with mixed type ED.

Of the 40 patients given combined therapy, 17 (43%) reported adverse effects, including penile pain in nine, headache in eight, facial flushing in 10, dyspepsia in two, nasal congestion in two and dizziness in two.

Table 3 also shows the comparison between responders and non-responders in EDITS score and EDITS index, where there

Table 1 Characteristics before treatment of 40 patients, with the vascular diagnosis.

Variable	Mean (SD) (range) (n)				
	All	Normal (5)	Arterial (5)	VOD (26)	Mixed (4)
SHIM-5	7.4 (0.8) (6–9)	8.4 (0.9) (7–9)	7.2 (0.4) (7–8)	7.3 (0.8) (6–9)	7.3 (0.9) (6–8)
<i>P</i>	0.03 ^a	–	0.05 ^b	0.01 ^b	0.08 ^b
PSV (cm/s)	36.9 (13.1) (15.5–63)	49.0 (17) (30.4–63)	18.6 (4.4) (15.5–26)	39.6 (10.2) (30–62)	28.1 (0.2) (28–28.4)
<i>P</i>	< 0.001 ^a	–	< 0.001 ^b	0.1 ^b	0.01 ^b
EDV (cm/s)	7.1 (2.8) (1.9–18)	4.2 (0.7) (3–4.6)	3.3 (0.9) (1.9–4)	7.9 (2.3) (5.7–18)	9.8 (1.9) (7.7–12)
<i>P</i>	< 0.001 ^a	–	0.08 ^b	0.001 ^b	0.001 ^b
RI	0.79 (0.08) (0.57–0.95)	0.89 (0.05) (0.84–0.95)	0.81 (0.060) (0.76–0.9)	0.79 (0.04) (0.71–0.87)	0.65 (0.07) (0.57–0.72)
<i>P</i>	< 0.001 ^a	–	0.02 ^b	< 0.001 ^b	< 0.001 ^b
Time to erection (min)	10.5 (3.4)	8 (2.7)	13 (4.4)	12.5 (3.1)	13.6 (2.5)
<i>P</i>	0.03 ^a	–	0.04 ^b	0.02 ^b	0.03 ^b
Duration of erection, min	34.9 (19)	36 (5.5)	27 (9.7)	28.1 (8.8)	22.5 (5)
<i>P</i>	0.1 ^a	–	0.2 ^b	0.1 ^b	0.05 ^b
EHS	2.3 (0.8)	3.2 (0.4)	2.2 (0.8)	2.3 (0.7)	1.5 (0.6)
<i>P</i>	0.005 ^a	–	0.05 ^b	0.01 ^b	0.001 ^b
Rigidity response, grade 3 or 4					
Positive		5	2	10	0
Negative		0	3	16	4
<i>P</i>	0.02 ^c				

^a Anova.

^b Anova, post hoc, Dunnett *t* (two-sided) *P* vs. normal responders.

^c Kruskal–Wallis test.

Table 2 Comparison between variables before and after treatment in 28 men who improved.

Variable	Before	After	<i>P</i> *
SHIM-5 score	7.7 (0.8)	21.8 (1.1)	<0.001
Time to erection (min)	11.2 (3.1)	7.9 (2.5)	<0.001
Duration of erection (min)	31.4 (7.6)	45.7 (12.6)	<0.001
EHS	2.5 (0.7)	3.6 (0.5)	<0.001
PSV (cm/s)	38.2 (13.4)	50 (11.4)	<0.001
EDV (cm/s)	6.7 (2)	3.6 (0.9)	<0.001
RI	0.80 (0.08)	0.91 (0.04)	<0.001

* Student's *t*-test for paired samples.

was a significant difference between responders and non-responders (EDITS score 2.7 vs. 1.7, and EDITS index 66.4% vs. 40.3%, *P* < 0.001 for each).

Discussion

The vascular, endocrine and neuronal systems are involved in the normal erectile function, and in men with ED one or more of these systems are deficient or damaged [1]. An essential part in erectile physiology is complete cavernous smooth muscle relaxation, which is regulated by cytosolic Ca²⁺ levels through two second-messenger systems involving cGMP and cAMP [16]. Pharmacological manipulation of these second-messenger pathways is currently used in the treatment of ED. In the present study we investigated the haemodynamic findings in 40 men not responding to sildenafil and ICI of PGE1, and tried

to manage them with combined chronic low daily dose of sildenafil and ICI of triple-agent therapy, not on-demand use and with no dose increments. The underlying haemodynamic findings in non-responders to sildenafil [17] and ICI of vasoactive drugs has been investigated previously [18,19]. The common underlying vascular abnormalities were corporal VOD alone or combined with arterial insufficiency. These abnormalities were the causes of failure, and are very difficult to treat, as those cases were predicted to be non-responders according to Mullhall et al. [19]; they stated that the presence of any degree of venous leak resulted in reduced efficacy of sildenafil, with only five of 46 (11%) patients responding to sildenafil. Also, corporeal VOD alone or combined with arterial disease is the specific haemodynamic abnormality causing no response to intracavernous pharmacotherapy [18]. Trials to treat these cases with combined therapy of sildenafil and vasoactive drugs was tried previously, but these studies used dose increments and on-demand therapy [7].

In the present study, in 40 patients with ED not responding to prolonged and challenging doses of sildenafil and ICI of PGE1, the most common haemodynamic abnormalities were VOD (26/40, 65%), pure arterial insufficiency (5/40, 13%) and mixed VOD and arteriogenic (4/40, 10%); this finding is in agreement with the findings of many authors investigating the underlying causes of lack of response. Martins and Padma-Nathan [18] found that 49% (34/69) of non-responders to ICI had VOD alone or combined with arterial disease, and this is the specific haemodynamic abnormality causing no response to ICI, while pure arterial insufficiency was found

Table 3 Differences between responders and non-responders.

Mean (SD) variable	Responders, 28 (70)	Non-responders, 12 (30)	<i>P</i> *
Age	46.1 (8.9)	61.3 (9.3)	<0.001
Duration of ED on previous	14.4 (8.2)	22.3 (7.9)	0.007
<i>Therapy (months)</i>			
SHIM-5 before	7.7 (0.8)	6.8 (0.6)	0.001
SHIM-5 after	21.8 (1.1)	17 (3.1)	<0.001
Time to erection (min)	7.9 (2.5)	11.7 (3.3)	<0.001
Duration of erection (min)	45.7 (12.6)	27.5 (7.5)	<0.001
EHS	3.6 (0.5)	1.9 (0.3)	<0.001
PSV (cm/s)	50 (11.4)	31.9 (7.8)	<0.001
EDV (cm/s)	3.6 (0.9)	8.1 (1.9)	<0.001
RI	0.91 (0.04)	0.74 (0.06)	<0.001
Mean EDITS score	2.7 (0.2)	1.7 (0.2)	<0.001
Standardised EDITS (%)	66.4 (4.9)	40.3 (4.3)	<0.001
<i>EDITS questionnaire items</i>			
Q1 Overall satisfaction	3 (0.5)	1.2 (0.4)	<0.001
Q2 Patient's expectations	3 (0.7)	2.5 (0.5)	0.030
Q3 Likely to continue	2.7 (0.7)	1.8 (0.8)	0.002
Q4 Ease of use	2.5 (0.6)	2.3 (0.7)	0.400
Q5 Satisfaction with onset	3.2 (0.5)	1.4 (0.5)	<0.001
Q6 Duration of action	3.2 (0.5)	1.8 (0.6)	<0.001
Q7 Confidence	3.1 (0.4)	1.6 (0.5)	<0.001
Q8 Patient's-rated partner satisfaction	2.2 (0.7)	1.9 (0.8)	0.200
Q9 Partner's desire to continue treatment	1.7 (0.6)	1.3 (0.5)	0.060
Q10 Naturalness of erection	2.5 (0.7)	1.4 (0.5)	<0.001
Q11 Hardness vs. before treatment	3.4 (0.5)	1.7 (0.5)	<0.001
EDITS score	2.7 (0.2)	1.7 (0.2)	<0.001
EDITS index	66.4 (4.9)	40.3 (4.3)	<0.001

* Student's *t*-test for unpaired samples.

in 16/69 (23%). The vascular abnormalities found in sildenafil non-responders were investigated in the study of Huang and Hsieh [17], where they found VOD in 16/38 (45%), mixed VOD and arteriogenic in three (8%), pure arterial in nine (24%) and normal vascular parameters in nine (24%). They concluded that veno-occlusive ED was the commonest type in sildenafil non-responders and associated with poor penile rigidity.

For the rigidity response in the present study (Table 1), poor penile rigidity was found in 58% of men (23/40) and rigidity response grade 3 and 4 was found in all patients with normal haemodynamics, in two of five of those with arterial insufficiency and 39% (10/26) of those with VOD, while all patients with mixed VOD and arterial insufficiency had no rigidity response grade 3 or 4. These results were comparable with the previously cited studies [17,18], where rigidity response grade 3 or 4 was found in a third of those with arterial insufficiency, 35% of those with VOD and 44% of those with normal response, while none of those with mixed vascular abnormality had positive response (grade 3 or 4) in the study of Huang and Hsieh [17]. The quality of erectile response to intracavernous pharmacological stimulation was found by Martins and Padma-Nathan [18] in 15 men with VOD to be poor or none in four (25%), adequate in three (20%) and excellent in eight (53%); in 19 men with mixed vascular types, poor or none in 12 (63%), adequate in three (16%) and excellent in four (21%); while 16 patients with arterial disease had an adequate response in 11 (69%) and excellent in five (31%). Rigid erection is not always associated with normal haemodynamics and it can coexist with some degree of vascular impairment. Hatzichristou et al. [20] hypothesised that haemodynamic integrity might not always indicate the presence of a functional/rigid erection and other factors can also contribute to penile rigidity.

A positive rigidity response with arterial insufficiency can be explained by the presence of an intact veno-occlusive mechanism that can maintain an erection response despite arterial insufficiency [21]. The status of penile erection must be interpreted with EDV and RI at the same point, and this agrees with the conclusion of Chiou et al. [13].

In the present study, we used chronic combined therapy with 25 mg of sildenafil citrate daily and 0.25 mL of a trimix solution of three vasodilators for ICI twice weekly (1 mL of solution containing 18.7 mg papaverine, 6.25 µg PGE1 and 0.62 mg phentolamine) for 8 weeks to enhance smooth muscle relaxation of the corpus cavernosum. The aim of this combination was to target many of the systems responsible for the erectile process, and using low doses in the combination to minimise side-effects. PDE-5 inhibitors maintain an erection by inhibiting the catabolism of cGMP with activation of the NO-cGMP pathway by sexual stimulation [6]. PGE1 induces relaxation of the cavernous smooth muscle and dilatation of cavernous arteries by increasing the intracellular cAMP concentration [22]. Papaverine increases the production of cAMP and cGMP by an inhibitory action on PDE, although papaverine acts at many levels, leading to a very complex mode of action in the smooth muscle [23]. The combination of oral sildenafil and ICI with trimix significantly increased the levels of cGMP and cAMP in the cavernosa but not in the peripheral blood plasma [8]. Also trimix solution might be helpful to overcome a false-positive diagnosis of VOD due to anxiety, which represents the major pitfall of this procedure [24].

In the present study, there was an improvement in 28 of the 40 men (70%) after treatment by combined therapy with sildenafil and trimix ICI for 8 weeks (Table 3); this combination salvaged ≈70% of patients not responding to sildenafil on-demand use with increasing doses up to 100 mg, and those with a suboptimal response to ICI with PGE1 as monotherapy. Comparing values before and after treatment in these 28 men, there was a significant improvement in haemodynamic values, SHIM-5 score, time to and duration of erection and EHS (Table 2).

McMahon et al. [7] studied the ability of sildenafil to salvage patients in whom ICI therapy failed. They reported a 66% salvage rate in patients receiving sildenafil combined with triple agent ICI therapy, but they found that the effect of combined therapy was no better in these men than with sildenafil alone. Our study differs from that study in that they used on-demand sildenafil up to 100 mg at 1 h before and triple-agent ICI 10 min before the planned sexual intercourse, while in the present study we used the combination of a chronic fixed daily low-dose of sildenafil citrate and twice weekly triple-agent ICI in a low-dose combination to reduce side-effects.

For the vascular aetiology in the 12 non-responders (Table 2), two of five had arterial insufficiency, nine of 26 had VOD (35%) and one of four had mixed type ED. These results agree with the previous studies assessing the underlying abnormalities in non-responders [17–19], i.e. VOD alone or combined with arterial disease is the most common abnormality underlying the lack of response.

Adding other factors such as age and duration spent under ineffective therapy, the difference between responders and non-responders (Table 2) was significant for age and duration of ED under previous therapy, where responders were younger and with shorter duration of ED than non-responders. Also, their pretreatment SHIM-5 scores were higher. The EDITS score after treatment was also significantly different, at 66.4% vs. 40.3% for non-responders ($P < 0.001$). Age and the competence of smooth muscle relaxation to vasoactive agents might play a major role in the erectile response to treatment in the present study, i.e. the mean age of patients in the non-responder group was 15 years greater than in the responder group.

All patients must be made aware that combined therapy has greater risks and side-effects because of synergy. McMahon et al. [7] reported adverse effects in 20 of 41 men (49%) after combined therapy with sildenafil and triple-agent ICI, including penile pain in 15, headache in 15, facial flushing in 12, dyspepsia in seven, nasal congestion in three, dizziness in 12 and syncope in one. Adverse effect rates in the present study were slightly lower than reported by McMahon et al. [7], possibly due to the use of smaller doses in our combined therapy, where of the 40 patients given combined therapy, 17 (43%) reported adverse effects, including penile pain in nine, headache in eight, facial flushing in 10, and two each with dyspepsia, nasal congestion or dizziness. These results suggest that low-dose trimix provides stronger stimuli to the penile vasculature than low-dose PGE1 [25].

Analysis of individual EDITS items (Table 3) showed that EDITS scores for responders vs. non-responders were significant for overall satisfaction (Q1, EDITS score 3 vs. 1.2, $P < 0.001$), met the patients' expectations (Q2, EDITS score 3 vs. 2.5, $P = 0.03$) and likely to continue (Q3, EDITS score 2.7 vs. 1.8, $P = 0.002$). Responders were satisfied with the onset and duration of action (Q5, EDITS score 3.2 vs. 1.4,

and Q6, EDITS score 3.2 vs. 1.8, $P < 0.001$ for each) and confidence in ability to be engaged in sexual activity (Q7, EDITS score 3.1 vs. 1.6, $P < 0.001$). Most responders do not care about the naturalness of erection but found the same hardness as before they had the ED problem, while most non-responders found it somewhat unnatural on therapy and less hard than before they had ED (Q10, EDITS score 2.5 vs. 1.4; Q11 EDITS score 3.4 vs. 1.7, $P < 0.001$ for each). Both groups found the treatment easy to use (Q4) and most partners were neither satisfied nor dissatisfied (Q8) and preferred to stop treatment (Q9); this might be due to cultural aspects in eastern countries (Table 3). It is possible that although a treatment might produce an excellent erection, a patient might rate the treatment as unsatisfactory because the erection was artificially induced, painful to create, failed to enhance the patient's sense of sexual confidence or masculinity, or was unacceptable to the partner [14].

There were some limitations to the present study. First, there were relatively few patients; more patients are needed. Second, a longer follow-up is needed to document the long-term efficacy of combined therapy.

In conclusion, chronic use of trimix and daily low-dose sildenafil improves penile haemodynamics in patients with ED not responding to on-demand PDE-5 inhibitors or ICI of PGE1 monotherapy.

References

- [1] Lue TF. Erectile dysfunction. *N Eng J Med* 2000;**342**:1802–13.
- [2] Lewis RW, Fugl-Meyer KS, Bosch R, Fugl-Meyer AR, Laumann E, Lizza E, et al. Epidemiology/risk factors of sexual dysfunction. *J Sex Med* 2004;**1**:35–9.
- [3] Lue TF, Giuliano F, Montorsi F, Rosen RC, Andersson KE, Althof S, et al. Summary of the recommendations on sexual dysfunctions in men. *J Sex Med* 2004;**1**:6–23.
- [4] Mulhall JP, Goldstein I, Bushmakin AG, Cappelleri JC, Hvidsten K. Validation of the erection hardness score. *J Sex Med* 2007;**4**:1626–34.
- [5] Mulhall JP, Althof SE, Brock GB, Goldstein I, Jünemann KP, Kirby M. Erectile dysfunction. Monitoring response to treatment in clinical practice – recommendations of an international study panel. *J Sex Med* 2007;**4**:448–64.
- [6] Padma-Nathan H, Christ G, Adaikan G, Becher E, Brock G, Carrier S, et al. Pharmacotherapy for erectile dysfunction. *J Sex Med* 2004;**1**:128.
- [7] McMahon CG, Samali R, Johnson H. Treatment of intracorporeal injection nonresponse with sildenafil alone or in combination with triple intracorporeal injection therapy. *J Urol* 1999;**162**:1992.
- [8] Park JK, Park JS, Jeon SB, Cui WS, Kim SZ, Kang KK, et al. Why a combined intracavernosal injection with trimix and oral sildenafil is reliable therapy in the ultrasonographic evaluation of erectile dysfunction. *BJU Int* 2008;**102**:993–7.
- [9] Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999;**11**:319–26.
- [10] Ramanathan R, Mulhall J, Rao S, Leung R, Martinez Salamanca A, Mandhani A, et al. Predictive correlation between the International Index of Erectile Function (IIEF) and Sexual Health Inventory for Men (SHIM): implications for calculating a derived SHIM for clinical use. *J Sex Med* 2007;**4**:1336–44.
- [11] Montorsi F, Salonia A, Zanoni M, Pompa P, Cestari A, Guazzoni G, et al. Current status of local penile therapy. *Int J Impot Res* 2002;**14**(Suppl. 1):S70–81.
- [12] Aversa A, Isidori AM, Caprio M, Cerilli M, Frajese V, Fabbri A. Penile pharmacotesting in diagnosing male erectile dysfunction. Evidence for lack of accuracy and specificity. *Int J Androl* 2002;**25**:6–10.
- [13] Chiou RK, Pomeroy BD, Chen WS, Anderson JC, Wobig RK, Taylor RJ. Hemodynamic patterns of pharmacologically induced erection: evaluation by color Doppler sonography. *J Urol* 1998;**159**:109–12.
- [14] Althof SE, Corty EW, Levine SB, Levine F, Burnett AL, McVary K, et al. EDITS. Development of questionnaires for evaluating satisfaction with treatments for erectile dysfunction. *Urology* 1999;**53**:793–9.
- [15] Brislin RW. Back-translation for cross-cultural research. *J Cross Cult Psychol* 1970;**1**:185–216.
- [16] Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. In: Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. *Campbell's urology*. 9th ed. Philadelphia: WB Saunders; 2007. p. 1653–5.
- [17] Huang ST, Hsieh ML. Different hemodynamic responses by color Doppler ultrasonography studies between sildenafil non-responders and responders. *Asian J Androl* 2007;**9**:129–33.
- [18] Martins FE, Padma-Nathan H. Diffuse veno-occlusive dysfunction. The underlying hemodynamic abnormality resulting in failure to respond to intracavernous pharmacotherapy. *J Urol* 1996;**156**:1942–6.
- [19] Mulhall J, Barnas J, Aviv N, Anderson M, Parker M. Sildenafil citrate response correlates with the nature and the severity of penile vascular insufficiency. *J Sex Med* 2005;**2**:104–8.
- [20] Hatzichristou DG, Hatzimouratidis K, Tzortzis V, Apostolidis A, Bekos A, Ioannidis E. Normal hemodynamic parameters do not always predict the presence of a rigid erection: a quantitative assessment of functional erectile impairment. *Int J Impot Res* 2003;**15**:99–104.
- [21] Pescatori ES, Hatzichristou DG, Namburi S, Goldstein I. A positive intracavernous injection test implies normal venoocclusive but not necessarily normal arterial function: a hemodynamic study. *J Urol* 1994;**151**:1209–16.
- [22] Alexandre B, Lemaire A, Desvaux P, Amar E. Intracavernous injections of prostaglandin E1 for erectile dysfunction: patient satisfaction and quality of sex life on long-term treatment. *J Sex Med* 2007;**4**:426–31.
- [23] Shamloul R, Atteya A, Elnashaar A, Gadallah A, Zohdy W, Abdelsalam W. Intracavernous sodium nitroprusside (SNP) versus papaverine/phentolamine in erectile dysfunction. A comparative study of short-term efficacy and side-effects. *J Sex Med* 2005;**2**:117–20.
- [24] Gontero P, Sriprasas S, Wilkins CJ, Donaldson N, Muir GH, Sidhu PS. Phentolamine re-dosing during penile dynamic colour Doppler ultrasound. A practical method to abolish a false diagnosis of venous leakage in patients with erectile dysfunction. *Br J Radiol* 2004;**77**:922–6.
- [25] Nandipati K, Raina R, Agarwal A, Zippe CD. Early combination therapy. Intracavernosal injections and sildenafil following radical prostatectomy increases sexual activity and the return of natural erections. *Int J Impot Res* 2006;**18**:446–51.