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Comparison of the clinical efficacy of daily use of L-arginine, tadalafil and combined L-arginine with tadalafil in the treatment of elderly patients with erectile dysfunction

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Abstract

This study aimed to evaluate the efficacy of the daily oral administrations of L-arginine, tadalafil and combined L-arginine with tadalafil in treatments of elderly patients with erectile dysfunction (ED). It was designed as a single-blind placebo-controlled clinical trial. It was conducted on 120 male patients aged ≥60 years old with ED. Patients were randomised classified into four groups (n = 30 each). Oral daily use of L-arginine (5 g), tadalafil (5 mg), combined L-arginine (5 g) with tadalafil (5 mg) and placebo were taken for 6 weeks in each group of patients respectively. Patients were assessed before and after treatments using the Sexual Health Inventory for Men (SHIM) questionnaire and total serum testosterone. The means of Q1–5, total scores of SHIM and total testosterone, in L-arginine, tadalafil and combined L-arginine with tadalafil groups were significantly higher after treatments (p = .001). Combined L-arginine with tadalafil group had the highest SHIM scores and levels of total testosterone. This clinical trial deduced that the combined daily use of L-arginine with tadalafil therapy for elderly male patients with ED could significantly increase the SHIM scores and levels of total testosterone in comparison to L-arginine, or tadalafil alone.

KEYWORDS

elderly, erectile dysfunction, tadalafil

1 | INTRODUCTION

Erectile dysfunction (ED) is defined as a persistent or recurrent inability to obtain and/or maintain sufficient penile erection for satisfactory sexual intercourse. The prevalence of ED is enhanced by ageing, and in general, ED is less than 10% among males aged <40 years, less than 15% among males aged 40–49 years, 20%–30% among males aged 50–69 years, 20%–40% among males aged 60–69 years, and 50%–100% among males aged ≥70 years (McCabe et al., 2016).

The risk factors for ED may be classified into four categories, including (a) cardiovascular and metabolic disorders (such as diabetes mellitus, hypertension, hyperlipaemia and obesity), (b) andrological or urological diseases (such as lower urinary tract symptoms), (c) psychosomatic and psychiatric disorders (such as depression, psychological stress and antidepressants) and (d) lifestyle factors (such as smokers and sedentary lifestyle) (Beutel, Weidner, & Brahler, 2006; McMahon, 2019; Nguyen, Gabrielson, & Hellstrom, 2017).

Penile erection is a complex phenomenon that denotes a delicate organised balance among vascular, neurological and tissue compartments. It comprises penile arterial dilation, smooth muscle relaxation of trabecular tissues with stimulation of the mechanism of corporeal veno-occlusion (Gratzke et al., 2010).

L-arginine is the main nitric oxide (NO) precursor, which is the most essential vasoactive neurotransmitter required for penile smooth muscle relaxation (Chen et al., 1999; Maggi, Filippi, & Ledda, 2000). NO has a pivotal role in the improvement of endothelial function. NO enhances erectile function by increasing the

endogenous amino acids that are required for synthesis and the ideal production of NO. Also, it affects nitric oxide-soluble guanylyl cyclase-protein kinase G signalling, which includes the stimulation of calcium-dependent potassium channels or prevents the up-regulated RhoA/Rho-kinase pathway (Gur, Kadowitz, Trost, & Hellstrom, 2007). It has been found that dietary supplementations with L-arginine could play an essential role in the treatment of ED (Chen et al., 1999).

Phosphodiesterase type 5 inhibitors (PDE5Is) are well established as the main treatment for ED. PDE5Is act by decelerating the degradation by phosphodiesterase type 5 (PDE5) of cyclic guanosine monophosphate (cGMP), an essential regulator of intracellular calcium which has a pivotal role in the relaxation of smooth muscle and then an accumulation of blood in the corpora cavernosa needed for penile erection (Hatzimouratidis et al., 2016).

The efficacy of PDE5 inhibitors shows the significance of the nitric oxide–cGMP pathway through the inhibition of the degradation of the NO-generated cGMP. By selectively inhibiting the PDE-5, PDE-5 inhibitors thus conserve and maintain the NO-triggered enhance in cGMP, which boosts smooth muscle relaxation of cavernosal trabecular tissues (Fazio & Brock, 2004; Friebe & Koesling, 2003).

Tadalafil is a selective and powerful PDEI5. It was approved for clinical use in 2003 after sildenafil and vardenafil approvals. It is characterised by a rapid onset with a long duration of action (36 hr). Its efficacy is not influenced by food intake (Forgue, 2006).

Therefore, there is no consensus concerning the effects of L-arginine supplementation on ED, especially among older men and further studies are needed. So, this clinical trial aimed to evaluate the clinical efficacy of the daily administration of L-arginine, tadalafil and combined L-arginine with tadalafil in treatments of elderly patients with ED.

2 | PATIENTS AND METHODS

This study was designed as a single-blind placebo-controlled clinical trial. It was done on 120 male patients aged ≥60 years old with ED who were diagnosed according to the Sexual Health Inventory for Men (SHIM) questionnaire (total scores <22) (Shamloul, Ghanem, & Abou-zeid, 2004). They were recruited from patients attending the outpatient clinic of Andrology, Faculty of Medicine, South Valley University, Egypt between May 2018 and May 2019.

All included patients were underwent primary evaluations included complete medical and sexual histories, and then general medical and local genital examinations.

Patients with the following conditions were excluded from this clinical trial; (a) smoking, (b) diabetes mellitus, (c) hypertension (d) renal or hepatic diseases, (e) chronic prostatitis, (f) neurological diseases, (g) penile deformities or penile implants and (h) receiving any drugs for treatment of ED 6 months before recruitment.

Patients were randomised equally categorised into four treatment groups (30 patients each).They were distributed among the four groups utilising randomised encrypted cards, so, all the patients were blinded regarding the nature of the received medications.

Group 1 was given daily 5 g oral tablets of L-arginine for six weeks. Group 2 was given daily 5 mg oral tablets of tadalafil for six weeks. Group 3 was given daily 5 g oral tablets of L-arginine and 5 mg oral tablets of tadalafil for six weeks. Group 4 was given daily oral starch tablets as a placebo for six weeks.

Patients were advised to practice intercourse twice to three times weekly. They were assessed before and after six weeks of treatments by the SHIM questionnaire.

2.1 | Laboratory work-up

After 12 hr of fasting, venous blood samples were drawn from all included patients before and at the end of six weeks of treatment for total serum testosterone assessments between 8.00 and 12.00 a.m. (utilising Architect Plus i1000 SR, Abbot Diagnostics).

2.2 | Sample size calculations

The sample size was prospectively assessed utilising the equation of clinical randomised control trials (Charles, Giraudeau, Dechartres, Baron, & Ravaud, 2009). Utilising 85% power and a value of 0.05, the size of the sample was calculated to be 30 elderly male patients with ED in each group of treatment.

2.3 | Ethical considerations

This clinical trial was approved by the Ethical and Scientific Committee, Faculty of Medicine, South Valley University, Egypt. Informed consent was taken from all patients after complete clarification of the benefits and risks of this clinical trial.

2.4 | Statistical analysis

Statistical analysis was performed utilising SPSS software version 22 (Chicago, USA). The data were normally distributed and presented as mean ± standard deviation (*SD*). A paired *t* test was used to analyse the variables within each group before and after treatment. One-way ANOVA test was used to analyse the variables among the different groups before and after treatment. The significant *p* value was ≤.05.

3 | RESULTS

This study conducted on 120 male patients aged ≥60 years old with ED. Thirty-five patients were ruled out from this clinical trial (15 patients were smokers, 10 patients were DM on oral hypoglycaemic

therapy, 5 patients were hypertension on treatment and 5 patients refused to participate in the study). There were no statistically significant differences among the patients in the study groups regarding different demographic features ($p > .05$; Table 1).

The present clinical study reported that the means of Q1–5 and total scores of SHIM before treatments among study groups were insignificant ($p > .05$). (Table 2).

The means of Q1–5 and total scores of SHIM, in L-arginine, tadalafil or combined L-arginine with tadalafil groups were significantly improved after six weeks of treatments in comparison with the baseline values ($p = .0001$), while the means of Q1–5 and total scores of SHIM, in the placebo group, were insignificantly improved after treatments ($p > .05$). (Table 2).

After six weeks of treatments, the means of Q1–5 and total scores of SHIM among L-arginine, tadalafil, combined L-arginine with tadalafil and placebo groups were significantly improved (p value .0001) and the highest mean values of Q1–5 and total scores of SHIM were presented in combined L-arginine with tadalafil group. (Table 2).

This study reported that the means of total testosterone before treatments among the study groups were insignificant ($p > .05$). (Table 3).

The means of total testosterone, in L-arginine, tadalafil and combined L-arginine with tadalafil groups were significantly improved after six weeks of treatments in comparison with the baseline values ($p = .0001$), while the mean of total testosterone, in the placebo group, was insignificant after treatment ($p > .05$).

After six weeks of treatments, the means of total testosterone among L-arginine, tadalafil, combined L-arginine with tadalafil and placebo groups were significant ($p = 0.0001$), and the highest mean values of total testosterone were presented in combined L-arginine with tadalafil group. (Table 3).

4 | DISCUSSION

Apart from the general health, age is the main risk factor for ED in men (McCabe et al., 2016). The normal process of ageing with the age-associated risk factor may be the cause of high ED prevalence among elderly men. Systemic, structural and functional changes of the penis in elderly men may include hormonal changes (mostly decrease testosterone and enhance sex hormone-binding globulin that leading to reduction in testosterone bioavailability; Margolese, 2000), reduction in elastic fibres and enhancement in the collagen fibres of the tunica albuginea (Akkus et al., 1997), and molecular alterations (reduction in NO synthesis; Andrew & Mayer, 1999).

There is no consensus concerning the effects of L-arginine supplementation on ED, especially among elderly men patients. So, this study aimed to compare the clinical efficacy of the daily use of L-arginine, tadalafil and combined L-arginine with tadalafil in the treatment of elderly patients with ED.

This study reported that daily oral use of 5 g L-arginine treatment for male patients aged ≥60 years old with ED for six weeks could significantly increase scores of SHIM and levels of total testosterone. These findings in agreement with Chen et al., 1999 who found that daily use of L-arginine in patients with ED significantly increased serum testosterone levels and boosted erectile functions. Also, Mozaffari-Khosravi, Fallahi, & Afkhami-Ardekani, 2017 showed that daily oral administration of 5 g L-arginine for 4 weeks in diabetic men with ED significantly improved erectile function, sexual desire, sexual satisfaction, sexual pleasure and testosterone levels. El Taieb, Hegazy, & Ibrahim, 2019 reported that daily administration of L-arginine (5 g) for 8 weeks significantly increased the International Index of Erectile Function 5-item questionnaire (IIEF-5) scores and levels of total testosterone in male patients with diabetic ED.

This clinical trial showed that daily oral use of tadalafil (5 mg) for six weeks in male patients aged ≥60 years old with ED improved the SHIM scores and total testosterone levels. These findings were in agreement with Huang et al. 2010 who found that daily use of tadalafil 5 mg for 6–8 weeks significantly enhanced endothelial functions, erectile hardness and IIEF-5 scores in ED patients. Besides, Li et al. 2010 reported that daily administration of tadalafil 5 mg for 12 weeks significantly improved self-esteem, questionnaire of relationship and IIEF-5. Ozcan et al., 2017 found that daily use of 5 mg tadalafil significantly improved ED due to enhanced levels of total testosterone.

The current clinical study showed that the combined daily oral administration of L-arginine (5 g) with tadalafil (5 mg) for male patients aged ≥60 years old with ED for six weeks could significantly increase the scores of SHIM and levels of total testosterone in comparison with L-arginine alone, or tadalafil alone. These findings were in agreement with El Taieb et al., 2019 who showed that daily oral use of L- arginine with tadalafil for 8 weeks significantly enhanced the IIEF-5 scores and

TABLE 1 Comparison between study groups regarding demographic data

	L-arginine ($n = 30$)	Tadalafil ($n = 30$)	Combined L-arginine with tadalafil ($n = 30$)	Placebo ($n = 30$)	p value
Age (years) (mean ± *SD*)	65.53 ± 5.81	66.13 ± 6.10	66.33 ± 6.13	66.26 ± 6.4	.766
BMI (mean ± *SD*)	22.20 ± 1.10	22.63 ± 1.06	22.70 ± 1.08	22.66 ± 1.06	.40
Duration of ED (years) (mean ± *SD*)	4.20 ± 1.93	4.23 ± 1.92	4.30 ± 1.95	4.33 ± 1.88	.29

Note: Data were expressed as mean ± *SD*. One-way ANOVA test was used for comparison among the study groups. p value of ≤.05 was considered statistically significant.

Abbreviations: BMI, body mass index; *SD*, standard deviation.

TABLE 2 Comparison between study groups regarding SHIM questionnaire

Questions	L-arginine (*n* = 30)	Tadalafil (*n* = 30)	Combined L-arginine with tadalafil (*n* = 30)	Placebo (*n* = 30)	*p* value
Q 1					
Before treatment	1.93 ± 0.52	1.90 ± 0.54	1.90 ± 0.54	1.90 ± 0.54	.80
After treatment	3.73 ± 0.63	4.30 ± 0.70	4.53 ± 0.50	2.13 ± 0.34	.0001
p value	.0001	.0001	.0001	.10	
Q 2					
Before treatment	1.86 ± 0.72	1.90 ± 0.70	1.86 ± 0.72	1.96 ± 0.55	.57
After treatment	3.93 ± 0.73	4.26 ± 0.78	4.60 ± 0.49	2.20 ± 0.48	.0001
p value	.0001	.0001	.0001	.10	
Q 3					
Before treatment	1.90 ± 0.60	1.90 ± 0.60	1.90 ± 0.60	2.00 ± 0.52	.58
After treatment	3.93 ± 0.73	4.62 ± 0.78	4.66 ± 0.47	2.20 ± 0.48	.0001
p value	.0001	.0001	.0001	.13	
Q 4					
Before treatment	1.90 ± 0.60	1.90 ± 0.60	1.90 ± 0.60	2.02 ± 0.48	.37
After treatment	4.00 ± 0.74	4.33 ± 0.75	4.66 ± 0.47	2.03 ± 0.49	.0001
p value	.0001	.0001	.0001	.20	
Q 5					
Before treatment	1.90 ± 0.60	1.90 ± 0.60	1.90 ± 0.60	2.00 ± 0.52	.58
After treatment	3.93 ± 0.73	4.26 ± 0.78	4.70 ± 0.46	2.20 ± 0.48	.0001
p value	.0001	.0001	.0001	.13	
Total score (mean ± *SD*)					
Before treatment	9.19 ± 1.95	9.5 ± 1.19	9.46 ± 1.70	9.88 ± 1.97	.22
After treatment	19.52 ± 2.09	21.77 ± 2.30	23.15 ± 2.91	10.35 ± 1.98	.0001
p value	.0001	.0001	.0001	.10	

Note: Data were expressed as mean ± *SD*. Comparisons of variables within each group before and after treatment were performed using paired *t* test. One-way ANOVA test was used for comparison between the study groups before or after treatments. *p* value of ≤.05 was considered statistically significant

Abbreviations: *SD*, standard deviation; SHIM, Sexual Health Inventory for Men questionnaire.

TABLE 3 Comparison between study groups regarding total testosterone

	L-arginine (*n* = 30)	Tadalafil (*n* = 30)	Combined L-arginine with tadalafil (*n* = 30)	Placebo (*n* = 30)	*p* value
Before treatment (mean ± *SD*) (nmol/L)	11.33 ± 3.10	11.46 ± 3.39	11.60 ± 3.32	11.33 ± 2.90	.80
After treatment (mean ± *SD*) (nmol/L)	13.70 ± 4.11	20.50 ± 3.70	22.83 ± 3.70	11.43 ± 2.55	.0001
p value	.0001	.0001	0001	.52	

Note: Data were expressed as mean ± *SD*. Comparisons of variables within each group before and after treatment were performed using paired *t* test. One-way ANOVA test was used for comparison between the study groups before or after treatments. *p* value of ≤.05 was considered statistically significant.

Abbreviation: *SD*, standard deviation.

levels of total testosterone in comparison with L-arginine or tadalafil alone in patients with diabetic ED. Besides, El-Wakeel, Fouad, Saleem, & Saber-Khalaf, 2020 reported that daily oral use of L- arginine (3 g) with on-demand sildenafil (50 mg every other day) showed significantly increased IIEF-5 scores than sildenafil alone in patients with ED.

The exact mechanism of this enhancement in the total scores of the SHIM and total serum testosterone levels is not clear well. But, it could be related to that L-arginine supplementation improves erectile functions and thus enhances confidence in sexual activities. This positive response improves testosterone secretion from the testicular Leydig cells. Beside, L-arginine could increase

the synthesis and release of NO and increase testicular blood flow, which could lead to enhance the synthesis and secretion of testosterone and improve sexual performance (Lamm, 2009). Also, Yasuda et al. 2008 found that the increased NO concentration was by enhancing in cGMP release. The cGMP is a vasodilator that increases testicular blood flow as well as synthesis and secretion of testosterone in the Leydig cells.

In addition, NO enhances penile vasodilatation and blood flow by diffusing across the membrane of the smooth muscles and stimulating soluble guanylate cyclase of corpus cavernosum smooth muscle to generate cGMP, leading to an enzymatic cascade, which prevents calcium influx, reduces concentrations of cytosolic calcium and thus promotes cavernosal smooth muscle relaxation (Behrends, Steenpass, Porst, & Scholz, 2000). Besides, by selectively inhibiting the PDE-5, PDE-5 inhibitors thus conserve and maintain the NO-triggered enhance in cGMP that boosts smooth muscle relaxation of cavernosal trabecular tissues (Fazio & Brock, 2004; Friebe & Koesling, 2003).

This clinical study came up with many recommendations. Large sample-sized studies with long durations follow-up were needed. Additionally, evaluations of sexual satisfaction for both partners before and after treatments of elderly male patients with ED were recommended.

This clinical study concluded that the combined daily use of L-arginine with tadalafil therapy for elderly male patients with ED for 6 weeks could significantly increase the SHIM scores and total testosterone levels in comparison to L-arginine alone, or tadalafil alone.

CONFLICT OF INTEREST

None.

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