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Efficacy and safety of combination of tadalafil and aspirin versus tadalafil or aspirin alone in patients with vascular erectile dysfunction: a comparative randomized prospective study

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Abstract

Purpose We aimed to investigate the efficacy and safety of tadalafil, aspirin, and tadalafil + aspirin combination therapy in vascular erectile dysfunction (VED).

Methods A total of 336 patients were randomly divided into four groups (group 1, aspirin 100 mg/day, 126 patients; group 2, tadalafil 5 mg/day, 72 patients; group 3, tadalafil 5 mg + aspirin 100 mg, 72 patients; group 4, placebo, 66 patients). In all groups, the changes from baseline to end point in erectile function scores on the International Index of Erectile Function (IIEF-EF) and the number of patients who answered "yes" to questions 2 and 3 of the sexual encounter profile(SEP) were compared statistically.

Results The changes in IIEF-EF scores after treatment were 7.2 ± 4.4, 7.3 ± 4.3, 7.5 ± 4.4, and 2.0 ± 4.6 for group 1 ($p < 0.0001$), group 2 ($p < 0.0001$), group 3 ($p < 0.0001$), and group 4 ($p = 0.0204$), respectively. The change in SEP-2 ratios after treatment were 36.6%, 36.9%, 41.7%, and 9.4% for group 1 ($p < 0.0001$), group 2 ($p < 0.0001$), group 3 ($p < 0.0001$), and group 4 ($p = 0.2925$), respectively. The change in SEP-3 ratios after treatment was 46.6%, 49.2%, 53.7%, and 12.5% for group 1 ($p < 0.0001$), group 2 ($p < 0.0001$), group 3 ($p < 0.0001$), and group 4 ($p = 0.1456$), respectively. In group 2, both the number of patients who reported side effects ($p < 0.0001$) and stopped using the drug due to side effects ($p < 0.05$) were significantly higher than the control and others groups.

Conclusions Successful results were obtained by tadalafil and aspirin monotherapy and tadalafil + aspirin combination therapy in patients with VED. However, the least side effect was observed in the tadalafil + aspirin group. Aspirin can be used alone in the treatment of patients with VED, or combined with tadalafil to reduce side effects and increase success.

Keywords Erectile dysfunction · Tadalafil · Aspirin · Antiplatelet · Therapy

Abbreviations

ASA	Acetylsalicylic acid
CAD	Coronary artery disease
cAMP	Cyclic adenylate monophosphate
cGMP	Cyclic guanylate monophosphate
COX	Prostaglandin H synthase
DUS	Doppler ultrasonography
IIEF	International index of erectile function
MPV	Mean platelet volume
NO	Nitric oxide
PDE5i	Phosphodiesterase type 5 inhibitors
PSV	Peak systolic velocity
PAD	Peripheric artery disease
PG	Prostaglandin
SEP	Sexual encounter profile
TxA2	Thromboxane
VED	Vascular erectile dysfunction

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Introduction

Oral phosphodiesterase type 5 inhibitors (PDE5i) including avanafil, sildenafil, tadalafil, and vardenafil are the first-line erectile dysfunction (ED) therapies [1]. PDE5 inhibition does not necessarily spontaneously induce an erection;

rather, when coupled with sexual stimulation (visual, cerebral, or physical), PDE5i enhances the capacity to attain and maintain an erection [2]. PDE-5 hydrolyzes cyclic guanylate monophosphate (cGMP) specifically to 5′GMP, promoting successful corporeal vascular relaxation and penile erection during sexual stimulation [2, 3].

The recommended standard starting dose of Tadalafil is 10 mg. However, some studies report that the use of 5 mg Tadalafil every other day has the same effect [4–7]. Tadalafil's long half-life renders the agent suitable for once-daily administration. The approval of once-daily tadalafil signaled a paradigm shift in ED management. In clinical trials, once-daily tadalafil improved erectile function and sexual satisfaction [8].

Some studies have shown that platelet activity is increased in vascular ED (VED) [9–17]. However, so far, only one study has been conducted to investigate the efficacy of antiplatelet therapy in VED. Previously, we investigated the efficacy of antiplatelet (aspirin) therapy in VED and demonstrated that aspirin may be an effective and safe therapeutic option especially in patients with high mean platelet volume (MPV) [10].

MPV is a parameter which states platelet size that is easily measured by automated blood counters and routinely available at a relatively low cost and reflects indirectly platelet activity [9]. Large platelets are metabolically and enzymatically more active than small platelets and produce more thromboxane, known as the most potent vasoconstrictor agent. Increased platelet activity plays an important role in the atherosclerosis formation through mechanisms such as thrombocyte gathering, thromboxane synthesis, and expression of adhesion molecules [18, 19].

Some studies reported that platelets play a pivotal role in the pathogenesis of atherosclerosis and peripheral artery disease (PAD) [20, 21]. There is evidence showing an association between MPV and cardiovascular disease, PAD, and stroke [12, 21]. Platelet aggregation plays an important role in the pathogenesis of acute myocardial infarction. MPV, an indicator of platelet activation, has been reported to be higher in patients with coronary artery disease compared to healthy individuals, and as a possible independent risk factor for myocardial infarction [22]. Large platelet size is an independent predictor of increased risk for coronary artery disease (CAD) and PAD [20].

Aspirin has been known for many years and is widely used for antiplatelet therapy [9, 18]. Aspirin impairs platelet activation, implying that a prostanoid (PG) is involved in the activation process. However, the effect of aspirin on platelet PGs is an exceptional example of the general aspirin–PG relationship. The antiplatelet effects of aspirin endure for the entire life of the platelet. Aspirin shows its antiaggregant effect by reducing thromboxane A2 (TxA2) synthesis, which is a strong aggregant and vasoconstrictor agent. It also reduces TxA2 synthesis by irreversibly inhibiting Prostaglandin (PG) H synthase-1 (COX-1) and Prostaglandin H synthase-2 (COX-2) enzyme activities. PGH2 is the precursor of Thromboxane A2. Ultimately, the antithrombotic effect occurs as the inhibition of Prostaglandin and Thromboxane A2 synthesis with the use of aspirin [9, 18].

We have previously examined the efficacy of aspirin in VED [10]. In this study, which is a continuation of the previous study, we aimed to investigate the efficacy of tadalafil + aspirin combination therapy in VED.

Methods

The study protocol was approved by the institutional ethics committee of the School of Medicine, Istanbul Medipol University, Turkey (June 2015). Between June 2015 and April 2019, 294 patients were diagnosed with VED. In the first part of the study that previously published, patients were randomized to Aspirin and control group 2:1 according to the order of arrival [10]. Then, they were randomized to Tadalafil and Tadalafil + Aspirin group 1:1 according to the order of arrival. Thus, a total of four different groups were obtained. The first group received Aspirin 100 mg/day for 6 weeks (group 1; Aspirin 100 mg). The second group received Tadalafil 5 mg day for 6 weeks (group 2: Lifta®5 mg). The third group was given Tadalafil 5 mg/day + Aspirin 100 mg/day (group 3; Lifta®5 mg + Aspirin®100 mg). The fourth group received placebo (group 4; 100 mg/day).

A total of 347 patients who met the inclusion and exclusion criteria were diagnosed with VED(the inclusion and exclusion criteria of the study in Table 1). However, a total of 336 patients were randomized into groups, because 11 patients declined to participate in the study. A total of 316 patients completed the study due to patients who were excluded from the study. Two patients from the aspirin group and five patients from the Tadalafil group stopped using the drug because of side effects (Fig. 1).

All patients were subjected to the detailed medical history, physical examination, erectile function evaluation, laboratory evaluations, and penile color Doppler ultrasonography (pDUS). For the evaluation of erectile function, International Erectile Function Index (IIEF) was questioned twice during the first visit and after 6 weeks of treatment in all patients. The ED level was questioned by IIEF erectile function (EF) Domain scores (sum of questions 1–5 and 15). The patients were grouped according to their erectile function area scores as mild ED (17–25), moderate ED (11–16), and severe ED (6–10) [23]. Penile color Doppler evaluation was conducted on the basis of the criteria proposed by La Vignera et al. [21]. The patients were classified according

Table 1 The inclusion and exclusion criteria of the study

Inclusion criteria	Men with vascular ED
	> 18 years old
	IIEF-EF score < 26
	PSV < 35 cm/s
	MPV > 11
Exclusion criteria	Patients with neurogenic or endocrinological ED
	A history of pelvic trauma or surgery
	History of pelvic radiation
	Untreated endocrine disease (such as hypopituitarism, hypothyroidism, or hypogonadism)
	Recent history of stroke, spinal cord injury, or other significant central nervous system injuries
	Vascular risk factors for ED
	Diabetes, smoking, or hypertension (sBP > 170 or dBP > 100)
	Active infectious disease
	Malignancy (current treatment with cancer chemotherapy or antiandrogens)
	Renal or hepatic failure
	Clinically significant penile deformity
	Psychiatric diseases
	Unstable angina within prior 6 months
	Myocardial infarction
	Coronary artery disease (coronary artery bypass graft surgery or percutaneous coronary intervention within prior 90 days)
	Evidence of congestive heart failure within prior 6 months
	New significant conduction defect within prior 90 days
	Contraindication for Tadalafil (i.e. nitrate consumption)
	Contraindication for Aspirin (i.e., allergic reactions, stomach or intestinal ulcer, bleeding of the stomach or intestines, hematological diseases such as thrombotic thrombocytopenic purpura, hemophilia and Von Willebrand's Disease, and habit of drinking too much alcohol)

sBP systolic blood pressure, *dBP* diastolic blood pressure, *IIEF* International Index of Erectile Function, *MPV* mean platelet volume, *PSV* peak systolic velocity in penile color Doppler

to the peak systolic velocity (PSV) value obtained. According to these, PSV ≥ 35 cm/s values were accepted as normal (no arterial insufficiency). PSV < 25 cm/s, between 25 and 29 cm/s, and between 30 and 34 cm/s values were accepted as severe, moderate, and mild arterial insufficiency, respectively. However, all patients with PSV values < 35 cm/s were accepted to have vasculogenic ED and were included in the study. The patients with ED, the vasculogenic ED diagnosis of which was not confirmed with USG (with peak systolic velocity ≥ 35 cm/s), even though their IIEF-ED score was < 26, were excluded from the scope of this study. All patients were reevaluated for drug side effects after 1 week. However, no IIEF questionnaire was done on this assessment.

The total blood count, including hemoglobin (Hgb), white blood cell (WBC), red blood cell (RBC), platelet (PLT), and MPV parameters, were measured in the patient and control groups. All parameters were measured using commercially available assay kits (Sysmex Europe GmbH, Norderstedt, Germany) with an autoanalyzer (Sysmex XT 200i, Hamburg, Germany). Normal values for MPV according to this assay kits were 7.8–11. Blood samples were drawn from the antecubital vein and analyzed immediately (without freezing) after an overnight fasting period. The blood samples were collected in tubes containing dipotassium ethylenediaminetetraacetic acid. All of the measurements were performed immediately after venipuncture to prevent in vitro platelet activation (within 1 h of sampling).

Statistical analyses were performed with MedCalc statistical software (Version 16.4.3, MedCalc Software bvba, Ostend, Belgium). Descriptive statistics (mean ± standard deviation), Student's *t* test, and Chi-square test were used and analyzed the quantitative outcomes. Student's *t* test was used to compare the IIEF-EF results obtained at the first visit and after 6 weeks of treatment, and *p* values < 0.05 were considered statistically significant. A total of 347 patients were collected, 336 patients were randomized, and 316 patients who completed the study were analyzed. This sample size gave at least 95% power to detect clinically significant treatment differences (change from baseline score between

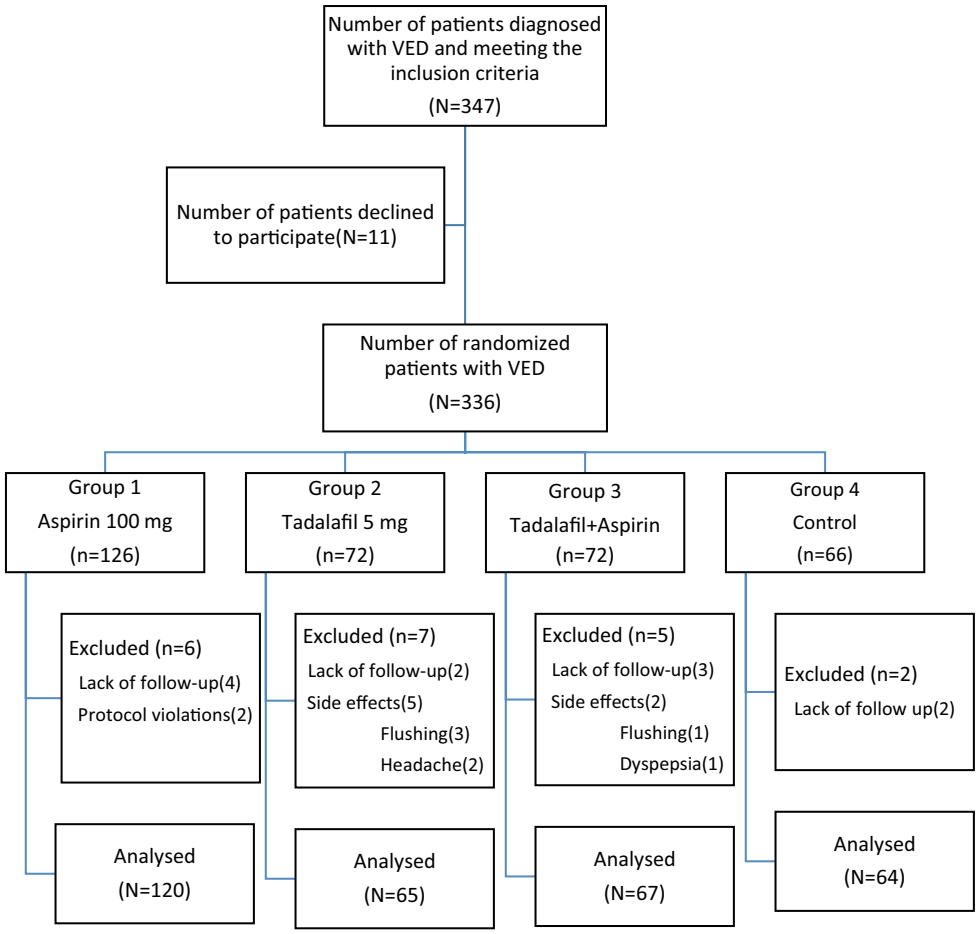

Fig. 1 Number of patients with VED included in the groups and completed the study (*VED* vasculogenic erectile dysfunction)

subjects, treated with aspirin, tadalafil, tadalafil + aspirin, and placebo) for IIEF-EF, SEP-2, and SEP-3.

Results

Basal parameters and pre-treatment and post-treatment IIEF-EF scores and SEP-2 and SEP-3 ratios are summarized in Table 2. Accordingly, pre-treatment IIEF-EF scores were 14.1 ± 4.9, 13.9 ± 4.2, 14.0 ± 5.3 and 14.3 ± 5.2 for group 1(aspirin), group 2 (tadalafil), group 3 (tadalafil + aspirin), and group 4 (placebo), respectively, after treatment 21.3 ± 4.1, 22.0 ± 4.4, 22.5 ± 4.3, and 16.3 ± 4.4. The changes in IIEF-EF scores were 7.2 ± 4.4, 7.3 ± 4.3, 7.5 ± 4.4, and 2.0 ± 4.63 for group 1 ($p < 0.0001$), group 2 ($p < 0.0001$), group 3 ($p < 0.0001$), and group 4 ($p = 0.0204$), respectively. The IIEF-EF scores were significantly increased in all groups except for the control group, but the highest increase was in group 3 ($p < 0.0001$).

The change in SEP-2 ratios after treatment were 36.6%, 36.9%, 41.7%, and 9.4% for group 1 ($p < 0.0001$), group 2 ($p < 0.0001$), group 3 ($p < 0.0001$), and group 4 ($p = 0.2925$), respectively. SEP-2 ratios were significantly increased in all groups except for the control group, but the highest increase was in group 3 ($p < 0.0001$).

The change in SEP-3 ratios after treatment were 46.6%, 49.2%, 53.7%, and 12.5% for group 1 ($p < 0.0001$), group 2 ($p < 0.0001$), group 3 ($p < 0.0001$), and group 4 ($p = 0.1456$), respectively. SEP-3 ratios were significantly increased in all groups except for the control group ($p < 0.0001$).

The number of patients who reported side effects were 24 (20%), 42 (60%), 18 (26%), and 10 (15.6%), for group 1, group 2, group 3, and group 4, respectively. The number of patients who discontinued medication due to side effects was 0 (0%), 5 (7.1%), 2 (2.9%), and 0 (0%) for group 1, group 2, group 3, and group 4, respectively (Table 3).

In group 2 (tadalafil group), the number of patients who reported side effects was significantly higher than the control group ($p < 0.0001$). The number of patients who stopped using the drug due to the side effects in group 2 was also significantly higher than the control group ($p < 0.05$).

Table 2 Baseline parameters and mean changes in IIEF-ED scores and SEP-2 and SEP-3 ratios with treatment in all groups

	Group 1 Aspirin ($N=120$)	Group 2 Tadalafil ($n=65$)	Group 3 Tadalafil + Aspirin ($n=67$)	Group 4 Control ($N=64$)	
Age	48.3 ± 12.5	46.5 ± 13.7	47.1 ± 14.3	47.7 ± 11.8	NS
WBC	8.17 ± 0.25	8.01 ± 0.22	7.96 ± 0.16	8.20 ± 0.19	NS
RBC	5.15 ± 0.22	5.19 ± 0.20	5.17 ± 0.26	5.20 ± 0.23	NS
Hgb	14.9 ± 0.62	15.01 ± 0.57	14.90 ± 0.51	15.14 ± 0.55	NS
PLT	186.27 ± 12.09	185.23 ± 12.02	187.96 ± 14.11	185.25 ± 12.13	NS
MPV	11.57 ± 0.17	11.55 ± 0.16	11.50 ± 0.17	11.54 ± 0.16	NS
IIEF-EF score					
Baseline	14.1 ± 4.9	13.9 ± 4.2	14.0 ± 5.3	14.3 ± 5.2	
Post-treatment	21.3 ± 4.1	22.0 ± 4.4	22.5 ± 4.3	16.3 ± 4.4	
Change in IIEF-EF	+ 7.2 ± 4.4	+ 7.3 ± 4.3	+ 7.5 ± 4.4	+ 2.0 ± 4.6	
	$p<0.0001$*	$p<0.0001$*	$p<0.0001$*	$p=0.0204$*	
	$p<0.0001$**	$p<0.0001$**	$p<0.0001$**		
"Yes'' responses. SEP-2, *n* (%)					
Baseline	62 (51.6%)	34 (52.3%)	36 (53.7%)	32 (50%)	
Post-treatment	106 (88.3%)	58 (89.2%)	64 (95.5%)	38 (59.3%)	
Change in SEP-	44 (36.6%)	24 (36.9%)	28 (41.7%)	6 (9.4%)	
	$p<0.0001$*	$p<0.0001$*	$p<0.0001$*	$p=0.2925$*	
	$p=0.0001$**	$p=0.0002$**	$p<0.0001$**		
"Yes'' responses. SEP-3, *n* (%)					
Baseline	38 (31.6%)	20 (30.7%)	21 (31.3%)	20 (31.2%)	
Post-treatment	94 (78.3%)	52 (80%)	57 (85.0%)	8 (43.7%)	
Change in SEP-3	56 (46.6%)	32 (49.2%)	(53.7%)	8 (12.5%)	
	$p<0.0001$*	$p<0.0001$*	$p<0.0001$*	$p=0.1456$*	
	$p<0.0001$**	$p<0.0001$**	$p<0.0001$**		

($p<0.05$, statistically significant)

ED erectile dysfunction, *IIEF* International Index of Erectile Function, *WBC* white blood cells, *RBC* red blood cells, *Hgb* hemoglobin, *PLT* platelet, *MPV* mean platelet volume, *NS* statistically nonsignificant, *SEP* sexual encounter profile, *S* statistically significant

*Comparison of baseline and post-treatment values (intra-group)

**Comparison with the control group

Discussion

Rosen et al. [24] reported that minimal clinically important differences (MCID) on the IIEF-EF score were 2, 5, and 7 for mild, moderate, and severe ED, respectively. In this study, we obtained 7.2, 7.3, and 7.5 increases in IIEF-EF scores in the aspirin, tadalafil, and tadalafil + aspirin groups, respectively. These findings suggest that aspirin and tadalafil are effective treatment options in the treatment of VED, but the best results are obtained by tadalafil + aspirin.

We have previously shown that aspirin may be a new therapeutic option in the treatment of VED, especially in patients with high MPV[10]. In this study also, we have shown that the best results in the treatment of VED can be obtained by combination of tadalafil + aspirin. In addition, one of the interesting results of this study is that; aspirin not only increases erectile function, but also decreases the number of patients who stopped using tadalafil because of side effects. In other words, aspirin increases the efficacy of tadalafil in VED treatment. How could aspirin do that? Aspirin should have reduced the side effects of tadalafil probably due to its analgesic and anti-inflammatory effects. Because the most common side effects of tadalafil are headache, back pain, myalgia, extremity pain, and flushing [25], and aspirin can also reduce such complaints.

Aspirin has been used for many years not only as an antiplatelet but also because of its analgesic and anti-inflammatory effect [26–28]. While aspirin is an analgesic and antiplatelet in low doses, it is also anti-inflammatory effect in high doses [28]. Therefore, aspirin may have reduced the side effects of tadalafil associated with pain and inflammation in patients in our study. Indeed, in our study, side effects such as headache, back pain, myalgia, extremity pain, and flushing were observed less in the tadalafil + aspirin group than the tadalafil group.

Table 3 Drug-related adverse effects observed in all groups

	Group 1 Aspirin ($N=120$) *n* (%)	Group 2 (Tadalafil) ($n=70$)[a] *n* (%)	Group 3 (Tadalafil + Aspirin) ($n=69$)[a] *n* (%)	Group 4 (Placebo) ($n=64$) *n* (%)
Dyspepsia	7 (5.8%)	4 (5.7%)	5 (7.2%)	2 (3.1%)
Nasal congestion	4 (3.3%)	2 (2.8%)	1 (1.4%)	1 (1.6%)
GERD	3 (2.5%)	2 (2.8%)	0	1 (1.6%)
Abdominal pain	3 (2.5%)	3 (4.2%)	1 (1.4%)	0
Dizziness	3 (1.6%)	0	1 (1.4%)	0
Influenza	2 (1.6%)	1 (1.4%)	0	0
Nasopharyngitis	1 (0.8%)	3 (4.2%)	1 (1.4%)	2 (3.1%)
Myalgia	1 (0.8%)	3 (4.2%)	1 (1.4%)	0
Headache	0	10 (14.2%)	3 (4.3%)	2 (3.1%)
Back pain	0	4 (5.7%)	2 (2.9%)	1 (1.6%)
Pain in extremity	0	3 (4.2%)	1 (1.4%)	0
Flushing	0	7 (10%)	2 (2.9%)	1 (1.6%)
Total	24(20%) $p=0.4651$*	42(60%) $p<0.0001$* $p<0.0001$**	18 (26.0%) $p=0.1427$*	10 (15.6%)
Drug stop (due to side effects)	0 (0%)	5 (7.1%) $p=0.0304$*	2 (2.9%) $p=0.1715$*	0 (0%)

GERD Gastroesophageal reflux disease

*Comparison with the control group

**Comparison with the groups 1 and 3

[a]Patients who terminated drug use due to side effects were also included (5 patients in group 2 and 2 patients in group 3)

There are variable rates in the literature about the side effects of tadalafil and the rates of patients discontinuing treatment due to these side effects. Seftel et al. [8] reported that the total adverse event rate was 38.2%, and the most common side effects were headache (8.8%), dyspepsia (4.7%), nasopharyngitis (2.5%), back pain (1.9%), myalgia (2.2%), nasal congestion (2.8%), and pain in extremity (2.5%) in the tadalafil 5 mg group. Buvat et al. [29] reported that the total adverse event rate was 31.1%, the rate of patients who terminated treatment due to side effects was 1.9%, and the most common side effects were headache (5.4%), dyspepsia (3.5%), myalgia (3.1%), abdominal pain in upper (3.1%), and back pain (1.9%) in the tadalafil 5 mg group. However, there are also studies reporting a higher rate of patients discontinuing treatment due to tadalafil side effects. Rajfer et al. [30] reported that tadalafil 2.5 mg and 5 mg, dosed once a day for 24 weeks, was well tolerated and significantly improved erectile function, but 6.3% of the patients in the tadalafil 2.5 mg group and 4.1% of the patients in the tadalafil 5 mg group discontinued treatment due to adverse events. In this study we presented, while the rate of patients who discontinued treatment due to adverse events was 7.1% in the tadalafil group, this rate was 2.9% in the tadalafil + aspirin group. In other words, aspirin significantly reduced the number of patients who discontinued treatment due to adverse events of tadalafil.

Penile erection is controlled by complex neural and vascular interactions that cause cavernosal smooth muscle relaxation [31, 32]. Prostaglandins also interact with nitric oxide (NO) in various ways and play a role in regulating penile erection. Nitric oxide is synthesized by neuronal (nNOS) and endothelial NO synthase (eNOS), and plays an important role in the cavernosal smooth muscle relaxation with the NO/cyclic guanosine monophosphate (cGMP) cascade [33]. Hafez et al. [31] detected a significantly increased expression in nNOS levels in ASA-treated diabetic rats. According to them, increased nNOS expression might be an important factor in improving ED in ASA-treated diabetic rat penises. They also reported that the intracavernosal pressure (ICP)/mean arterial blood pressure (MAP) ratio in the ASA-treated diabetic group was significantly higher than that of diabetic rats in in vivo studies. Most importantly, this normalized effect shows the protective effect of aspirin in diabetes. They said that, based on these findings, aspirin might be a novel therapeutic option in diabetic ED and might even be used for the prophylactic treatment of diabetic ED to preserve the erection capacity of patients [31].

Bornman et al. [34, 35] reported that platelets might play a significant role in hypercoagulability and fibrin deposition

during erection, and could be an important factor in the pathogenesis of aging impotence, and more importantly, aspirin might delay penile atherosclerosis.

The effect of aspirin on VED can be explained through these mechanisms. Because it is a cardioprotective agent that inhibits platelet activity, a decrease in vascular smooth muscle cell proliferation, and a reduction in proinflammatory mediators [26–28]. As a matter of fact, there are some clinical and experimental studies, showing that aspirin increases erectile function [10, 33, 35–38]. Argiolas et al. [33] reported that aspirin had beneficial effects on erectile function at the peripheral but not central level. In diabetic rats, aspirin has been found to normalize the diminished mean intracavernosal pressure/mean arterial blood pressure ratio required to recuperate erectile function [31]. In ex vivo studies, aspirin has been shown to improve arterial blood flow and to prevent hypercoagulation in the penis of the Chacma baboon during erection [35].

In vitro studies show that aspirin can protect and restore ED. This has been indicated by an improved relaxation response to acetylcholine, improvements in electrical field stimulation, and the presence of sodium nitroprusside in corpus cavernosum strips [31]. These vasoactive responses are mediated through the local generation of nitric oxide, acetylation of endothelial nitric oxide synthetase, and increased levels of neuronal nitric oxide synthase in penile vessels, and all are independent of the levels of cyclooxygenase I or II and the intracellular or extracellular calcium level. Interestingly, the concentration of aspirin that increases endothelial nitric oxide generation is compatible with the therapeutic range in humans. Therefore, aspirin is expected to improve vascular and neurogenic ED in therapeutic doses. This benefit is reflected by ED improvement in patients with bipolar disorder being treated with lithium, which can impair the NO-mediated relaxation of cavernosal tissue [36].

This benefit of aspirin on erectile function has also been shown clinically. In a randomized double-blind placebo-controlled trial of 32 male patients with "stable" bipolar disorder, significant advantages of aspirin over placebos were observed in reducing overall sexual dysfunction and improving erectile function [38]. Aspirin (240 mg/day) significantly improved the overall and intercourse satisfaction when compared to placebo treatment (63.9 vs. 14.4%) in 6 weeks after treatment without causing changes in the blood lithium level or disease severity. Aspirin improved all sexuality-related outcomes, scores in all domains, the severity category of erectile dysfunction, and the proportion of patients who had experienced minimal clinically important differences (MCID) in the erectile function domain. However, the largest effect of aspirin was observed in the erectile function domain, which is probably the main target of lithium. The authors of this study interpreted these findings as evidence for the safety and efficacy of aspirin in the treatment of several domains of lithium-induced sexual dysfunction in male patients with bipolar affective disorder [38].

Tadalafil has been observed to have an effect on the platelet activation. De Bone et al. [39] evaluated the effects of tadalafil on cyclic nucleotides(cGMP and cAMP) and soluble adhesion molecules (E- and P-selectin). In their study, the patients were divided into two groups on the basis of the presence or absence of cardiovascular risk factors such as dyslipidemia, hypertension, and smoking. Tadalafil administration induced a significant increase in cGMP levels in both groups. In contrast, cAMP significantly increased and P-Selectin decreased only in patients without cardiovascular risk factors. Tadalafil induced a beneficial effect on platelet activation in patients with ED without cardiovascular risk factors and this effect was not mediated by NO. Namely, the beneficial effect of tadalafil on platelet activation was independent of nitric oxide.

The results of these studies, which evaluate the effect of PDE5i on human vascular function, tissue cyclic nucleotides, platelet function, platelet aggregation, and nitric oxide, suggest that PDE5i and aspirin have partially similar effects at the cellular level. Indeed, the findings obtained from the study of Aversa et al. [40] also show that tadalafil has an antiaggregant effect similar to aspirin in the vascular endothelium. In this study, the changes occurring on the endothelial dysfunction parameters with the chronic tadalafil use were examined, and it was observed that there was a decrease in vascular cell adhesion molecules (VCAM), C-reactive protein (CRP), and Endothelin-1 (ET-1) levels, and there was an increase in the insulin level without any change in blood pressure and other laboratory parameters with the use of tadalafil. The fact that tadalafil leads to a decrease in VCAM indicates that it has an antiaggregant effect. Thus, oral PDE5i and Aspirin have similar effects, though partially.

More effective results were obtained with the daily use of tadalafil compared to the use of 20 mg before sexual intercourse [40]. This situation is attributed to increases in penile oxygenation obtained with the chronic use of tadalafil, and clinically dramatic increases are observed in the morning erections of these patients. Indeed, the basic logic of vascular rehabilitation in patients with ED is these increases in the penile oxygenation obtained with the chronic use. Aspirin with an antiaggregant effect may also increase penile oxygenation if one of the basic factors in the increase of the penile oxygenation obtained with the chronic tadalafil use is the VCAM, CRP, and ET-1 decreases in the vascular endothelium.

These clinical and experimental studies in the literature examining the relationship between tadalafil/aspirin and erectile function are consistent with our findings in this clinical study.

Conclusions

Successful results were obtained by tadalafil and aspirin monotherapy and tadalafil + aspirin combination therapy in patients with VED. However, the least side effect was observed in the tadalafil + aspirin group. Aspirin can be used alone in the treatment of patients with VED, or combined with tadalafil to reduce side effects and increase success. However, there is a need for multicenter, randomized, placebo-controlled, more extensive studies on this subject.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest in the study. Zeki Bayraktar declares that he has no conflict of interest. Selami Albayrak declares that he has no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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