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Antiplatelet (aspirin) therapy as a new option in the treatment of vasculogenic erectile dysfunction: a prospective randomized double-blind placebo-controlled study

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Abstract

Purpose To investigate the efficiency of antiplatelet (aspirin) therapy in vasculogenic erectile dysfunction (VED) patients with a high mean platelet volume.

Methods A total of 184 patients diagnosed with VED between the ages of 18 and 76 were randomly divided into two groups and treated for 6 weeks [group 1: 120 patients (mean age 48.3), aspirin 100 mg/day; group 2: 64 patients (mean age 47.7), placebo 100 mg/day]. 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 mean baseline IIEF-EF scores in groups 1 and 2 were 14.1 ± 4.9 and 14.3 ± 5.2, respectively ($p = 0.7966$), the number of patients who answered "yes" to SEP-2 was 62 (51.6%) in group 1 and 32 (50%) in group 2 ($p = 0.8366$), and the number of patients who answered "yes" to SEP-3 was 38 (31.6%) in group 1 and 20 (31.2%) in group 2 ($p = 0.9557$). In the aspirin group, the changes from baseline to end point in the IIEF-EF, SEP-2, and SEP-3 scores were 7.2, 36.6, and 46.6%, respectively. In the placebo group, these changes were 2.0, 9.4, and 12.5%, respectively. When compared with the placebo group, aspirin-treated subjects showed a significant improvement in all three efficacy measures ($p < 0.0001$).

Conclusions 100 mg of aspirin administered once a day significantly improved EF in men with VED.

Keywords Aspirin · Antiplatelet · Antithrombocytic · Erectile dysfunction · Treatment

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
PSV	Peak systolic velocity
PAD	Peripheric artery disease
PG	Prostaglandin
SEP	Sexual encounter profile
TxA2	Thromboxane
VED	Vasculogenic erectile dysfunction

Introduction

Erectile dysfunction (ED) is the inability to attain and/or maintain sufficient penile erection for satisfactory sexual intercourse [21]. ED has been classified as psychogenic, organic, or mixed because it is a multifactorial disease with a pathophysiology affected by causes that are vascular (peripheral and coronary artery disease, etc.), neurogenic (multiple sclerosis, Parkinson's disease, Alzheimer's disease, etc.), hormonal (hypothyroidism, hypogonadism, hyperprolactinemia, etc.), iatrogenic (cystectomy, prostatectomy, etc.), anatomic (trauma, etc.), and psychogenic [4, 8].

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Recent data show that more than 90% of ED cases in over 40 years old have an organic cause and that vascular diseases are the most common etiology. Although ED is a natural consequence of aging, its severity is directly related to vascular risk factors such as high blood pressure, atherosclerosis, coronary artery disease, smoking, dyslipidemia, and diabetes mellitus, all of which are associated with endothelial dysfunction [8].

Since the penis can be considered a barometer of the body's endothelial function, it is reasonable to identify vascular risk factors as direct causes of and contributors to ED. Therefore, ED may also be the first clinical presentation of any of these comorbidities, as vascular endothelium plays a pivotal role in regulating vascular homeostasis of the corpora cavernosa [8].

Some studies have reported that platelets play a pivotal role in the pathogenesis of atherosclerosis and peripheric artery disease (PAD). There is evidence of an association between mean platelet volume (MPV) and cardiovascular disease, PAD, and stroke. 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 (CAD) than in healthy individuals and may be an independent risk factor for myocardial infarction. Large platelet size is an independent predictor of increased risk for CAD and PAD [9, 18].

The antiplatelet effect of acetylsalicylic acid (ASA) has been known for many years, and it is widely used to treat cardiovascular diseases [11, 25]. Furuno et al. [14] reported that all doses of ASA suppressed platelet activity and at higher doses, endothelial-mediated arterial dilatation worsened. Aspirin decreases vascular smooth muscle cell proliferation and proinflammatory mediators and improves endothelium-dependent vasorelaxation mediated by nitric oxide (NO) [11, 14, 28]. 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 [18]. Aspirin exhibits its antiaggregant (antithrombocytic) 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 results from the synthesis of prostaglandin and thromboxane A2 being inhibited by aspirin [11].

Mean platelet volume (MPV) is an indicator of platelet size. It is easily measured by automated blood counters, it is routinely available at a relatively low cost, and it indirectly reflects platelet activity [19]. 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 atherosclerosis formation through mechanisms such as thrombocyte gathering, thromboxane synthesis, and expression of adhesion molecules [1, 9, 12].

Some recent studies have reported a relationship between high MPV values and VED [2, 5, 10, 15, 19, 22, 27]. However, to date, no studies have investigated the efficacy of antiplatelet therapy on VED. We hypothesize that aspirin improves erectile function (EF) in patients with ED. The aim of the present study was to assess the efficacy of aspirin in VED patients with high MPV values.

Methods

The study protocol was approved by the institutional ethics committee of the School of Medicine, Istanbul Medipol University, Turkey (01/06/2015-66291034-32). The study of 192 men too place from August 2015 to September 2017. Patients were randomized into two treatment groups at a 2:1 ratio according to the order of application. Group 1, with 126 patients, was given aspirin (100 mg/day) (Aspirin® 100 mg) for 6 weeks [11]. Group 2, with 66 patients, was given a placebo (100 mg/day). Placebo tablets were produced from starch and contained same ingredients as the aspirin tablets except acetylsalicylic acid.

Four patients in group 1 and two patients in group 2 were excluded because of a lack of follow-up. Two patients in group 1 were excluded because of protocol violations. A total of 184 patients who completed the study were subjected to detailed medical histories, physical examinations, erectile function evaluations, laboratory evaluations, and penile color Doppler ultrasonographies (pDUS). All patients were reevaluated for drug side effects after 1 week. However, IIEF questionnaire were not conducted at this time. ED level was evaluated with the sum of IIEF-EF scores (questions 1–5 and 15). Patients were grouped according to their scores as mild (17–25), moderate (11–16), and severe ED (1–10) [23].

Patients were questioned twice: during the initial visit and 6 weeks after treatment. Patients were asked sexual encounter profile (SEP) question 2 (Were you able to insert your penis into partner's vagina?) and SEP question 3 (Did your erection last long enough for you to have successful intercourse?). The study's co-primary efficacy measures were changes from baseline to end point in the IIEF-ED domain score and percentage of "yes" responses to SEP questions 2 and 3. All evaluations and analyses were performed by urologists and were double blind (both patients and urologists were blind to the study).

Penile color Doppler evaluation was conducted following La Vignera et al. [18]. Patients were

classified according to the peak systolic velocity (PSV). PSV ≥ 35 cm/s values were accepted as normal (no arterial insufficiency). PSV values of < 25, 25–29, and 30–34 cm/s were categorized as severe, moderate, and mild arterial insufficiency, respectively. Patients with PSV values < 35 cm/s were diagnosed with VED and were included in the study. Patients with ≥ 35 cm/s PSV were excluded from the study, even if their IIEF-EF scores were < 26.

Total blood count including hemoglobin (Hgb), white blood cell (WBC), red blood cell (RBC), platelet (PLT), and mean platelet volume (MPV) were measured in the patient and control groups. All parameters were measured by using commercially available assay kits (Sysmex Europe GmbH, Norderstedt, Germany) with an autoanalyzer (Sysmex XT 200i, Hamburg, Germany). Normal values for MPV according to these assay kits were 7.8–11 fL. Blood samples were drawn from the antecubital vein and analyzed immediately (without freezing) after overnight fasting. 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).

The study's inclusion and exclusion criteria are in Table 1. Statistical analyses were performed using MedCalc statistical software (Version 16.4.3, MedCalc Software bvba, Ostend, Belgium). The descriptive statistics (mean ± SD and percentages), Student's *t* tests, and Wilcoxon signed-rank tests were used to compare parametric and nonparametric values, respectively; p values < 0.05 were considered to be statistically significant.

The 184 subjects were randomized into two treatment groups at a 2:1 ratio (aspirin:placebo), which was calculated to provide at least 95% treatment effect ($p < 0.0001$) [4.1 (95% CI 3.7–6.2) for IIEF-EF, 29% (95% CI 14.9–42.9%) for SEP-2, and 34.6% (95% CI 19.1–48.8%) for SEP-3].

Results

The mean age in groups 1 and 2 was 48.3 ± 12.5 and 47.7 ± 11.8 years, respectively ($p = 0.7523$). MPV values were 11.57 ± 0.17 in the aspirin group and 11.54 ± 0.16 in the placebo group ($p = 0.4130$). In the aspirin group, the

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:
	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 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, or the 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

mean baseline IIEF-EF score—the number of the patients who answered "yes" to SEP-2 and SEP-3—was 14.1 ± 4.9, 62 (51.6%) and 38 (31.6%), respectively. In the placebo group, the mean baseline IIEF-EF score—the number of the patients who answered "yes" to SEP-2 and SEP-3—was 34 (60.7%) and 20 (35.7%), respectively. There was no significant difference between the two groups in terms of the age, MPV, baseline IIEF-EF scores, or SEP-2 and SEP-3 ratios (Table 2).

After treatment, mean scores for IIEF-EF, SEP-2, and SEP-3 in the aspirin group were 21.3 ± 4.1, 106 (88.3%), and 94 (78.3%), respectively. In the placebo group, the scores were 16.3 ± 4.4, 38 (59.3%), and 28 (43.7%), respectively. The changes in the aspirin group from baseline to end point in the three measures were 7.2 (difference between means), 36.6, and 46.6%, respectively. The same changes in the placebo group were 2.0 (difference between means), 9.4, and 12.5%. The change in IIEF-EF score was significantly higher in the aspirin group than in the placebo group ($p < 0.0001$). The change in "yes" responses to SEP-2 was significantly greater in the aspirin group (36.6%) than in the placebo group (9.4%) ($p = 0.0001$). The change in "yes" responses to SEP-3 was significantly greater in the aspirin group (46.6%) than in the placebo group (12.5%) ($p < 0.0001$). At the end of the study, 52 patients (43.3%) in the aspirin group and 18 patients (28.1%) in the placebo group had an IIEF-EF domain score > 25. The difference is statistically significant ($p = 0.0436$). While the increases in IIEF, SEP-2, and SEP-3 measures were statistically significant in the aspirin group, there was no significant difference in the placebo group. The aspirin group showed a significant improvement in all three efficacy measures ($p < 0.0001$).

For mild, moderate, and severe ED subgroups who took aspirin, the mean increases in IIEF-EF scores were 7.9, 10.1, and 3.6, respectively, but were lower in the placebo group: 3.3, 2.0, and 0.6 ($p < 0.0001$). IIEF-EF increases in the aspirin group for the mild and moderate ED subgroups were greater than minimal clinically important differences (MCID) as reported by Rosen et al. [24]. In the aspirin group, the changes in SEP-2 and SEP-3 were statistically significant in the mild and moderate ED subgroups ($p < 0.0001$), but not significant in the severe ED subgroup (Table 3).

None of the patients in the study reported worse sexual results after treatment. There were minimal gastric complaints such as dyspepsia and abdominal burning in five patients (4.1%) in the aspirin group ($p = 0.1015$). No drug-related severe adverse effects were observed.

Discussion

These findings suggest that aspirin may be a new treatment option in patients with VED, especially those with high MPV values. Rosen et al. [24] reported that minimal clinically important differences (MCID) on the IIEF-EF scale were 2, 5, and 7 for mild, moderate, and severe ED, respectively. This study's mean was higher, 7.2. This difference means there was a clinically significant increase in IIEF-EF for ED patients who took aspirin.

Penile erection is controlled by complex neural and vascular interactions that cause cavernosal smooth muscle relaxation [16, 29]. ASA is a cardioprotective agent that inhibits platelet activity, a decrease in vascular smooth

Table 2 Baseline characteristics of the patients in both groups

	Aspirin ($N = 120$)	Placebo ($N = 64$)	p values
Age ± SD (years)	48.3 ± 12.5	47.7 ± 11.8	0.7523
< 40	22 (18.3%)	12 (18.7%)	0.9470
40–49	42 (35%)	20 (31.2%)	0.6044
50–59	40 (33.3%)	22 (34.3%)	0.8915
≥ 60	16 (13.3%)	10 (15.6%)	0.6703
ED duration [*n* (%)]			
≥ 3 months and < 6 months	14 (11.6%)	8 (12.5%)	0.8579
≥ 6 months to < 12 months	60 (50%)	34 (53.1%)	0.6895
≥ 12 months	46 (38.3%)	22 (34.3%)	0.5933
MPV	11.57 ± 0.17	11.54 ± 0.16	0.2462
ED severity [*n* (%)]			
Mild (17–25)	56 (46.6%)	30 (46.8%)	0.9794
Moderate (11–16)	40 (33.3%)	22 (34.3%)	0.8915
Severe (1–10)	24 (20%)	12 (18.7%)	0.8327

ED erectile dysfunction, *EF* erectile function, *IIEF* International Index of Erectile Function, *n* number of subjects per category, *N* number of subjects in each treatment group, *MPV* mean platelet volume, *SD* standard deviation

Table 3 Changes in IIEF-ED scores and SEP-2 and SEP-3 ratios with treatment in all groups

All ED patients ($N = 184$)	Aspirin ($N = 120$)	Placebo ($N = 64$)	p values
Age (years ± SD)	48.3 ± 12.5	47.7 ± 11.8	0.7523
IIEF-EF score; baseline	14.1 ± 4.9	14.3 ± 5.2	0.7966
Post-treatment	21.3 ± 4.1	16.3 ± 4,4	< 0.0001
Change in IIEF-EF	+7.2 ± 4.4	+2.0 ± 4.6	< 0.0001
	$p < 0.0001$	$p = 0.0204$	
"Yes" responses, SEP-2, n (%); baseline	62 (51.6%)	32 (50%)	0.8366
Post-treatment	106 (88.3%)	38 (59.3%)	< 0.0001
Change in SEP-2	44 (36.6%)	6 (9.4%)	0.0001
	$p < 0.0001$	$p = 0.2925$	
"Yes" responses, SEP-3, n (%); baseline	38 (31.6%)	20 (31.2%)	0.9557
Post-treatment	94 (78.3%)	28 (43.7%)	< 0.0001
Change in SEP-3	56 (46.6%)	8 (12.5%)	< 0.0001
	$p < 0.0001$	$p = 0.1456$	
Mild ED patients ($n = 86$)	$n = 56$	$n = 30$	p values
Age, years ± SD	41.6 ± 9.3	40.9 ± 8.7	0.7346
IIEF-EF score; baseline	19.2 ± 4.3	19.6 ± 4.7	0.6916
Post-treatment	27.1 ± 4.4	22.9 ± 4.8	0.0001
Change in IIEF-EF	7.9 ± 4.3	3.3 ± 4.6	< 0.0001
	$p < 0.0001$	$p = 0.0093$	
"Yes" responses, SEP-2, n (%); baseline	34 (60.7%)	15 (50%)	0.3423
Post-treatment	54 (96.4%)	17 (56.6%)	< 0.0001
Change in SEP-2	20 (35.7%)	2 (6.6%)	0.0034
	$p < 0.0001$	$p = 0.6114$	
"Yes" responses, SEP-3, n (%); baseline	20 (35.7%)	12 (40%)	0.6959
Post-treatment	50 (89.2%)	16 (53.3%)	0.0002
Change in SEP-3	30 (53.5%)	4 (13.3%)	0.0003
	$p < 0.0001$	$p = 0.3059$	
Moderate ED patients ($n = 62$)	$n = 40$	$n = 22$	p values
Age, years ± SD	46.2 ± 10.4	45.7 ± 11.3	0.8612
IIEF-EF score; baseline score	14.6 ± 4.4	14.6 ± 4.5	1.000
Post-treatment	24.7 ± 4.5	16.6 ± 4.6	< 0.0001
Change in IIEF score	10.1 ± 4.2	2.0 ± 4.5	< 0.0001
	$p < 0.0001$	$p = 0.1523$	
"Yes" responses, SEP-2, n (%); baseline	19 (47.5%)	12 (54.5%)	0.6009
Post-treatment	39 (97.5%)	15 (68.1%)	0.0011
Change in SEP-2	20 (50%)	3 (13.6%)	0.0049
	$p < 0.0001$	$p = 0.3599$	
"Yes" responses, SEP-3, n (%); baseline	14 (35%)	6 (27.2%)	0.5328
Post-treatment	37 (92.5%)	9 (40.9)	< 0.0001
Change in SEP-3	23 (57.5%)	3 (13.6%)	0.0009
	$p < 0.0001$	$p = 0.3432$	
Severe ED patients ($n = 42$)	$n = 24$	$n = 12$	p values
Age, years ± SD	57.1 ± 8.9	56.5 ± 9.3	0.8521
IIEF-EF score; baseline score	8.7 ± 2.4	8.9 ± 2.3	0.8126
Post-treatment	12.3 ± 2.7	9.5 ± 2.4	0.0046
Change in IIEF score	3.6 ± 2.1	0.6 ± 2.0	0.0002
	$p < 0.0001$	$p = 0.5382$	
"Yes" responses, SEP-2, n (%); baseline	9 (37.5%)	5 (41.6%)	0.8145

Table 3 (continued)

Severe ED patients ($n = 42$)	$n = 24$	$n = 12$	p values
Post-treatment	13 (54.1%)	6 (50%)	0.8148
Change in SEP-2	4 (16.6%)	1 (8.3%)	0.5026
	$p = 0.2534$	$p = 0.4672$	
"Yes" responses, SEP-3, n (%); baseline	4 (16.6%)	2 (16.6%)	1.000
Post-treatment	7 (29.1%)	3 (25%)	0.7984
Change in SEP-3	3 (12.5%)	1 (8.3%)	0.7092
	$p = 0.3075$	$p = 0.6860$	

muscle cell proliferation, and a reduction in proinflammatory mediators [14, 28].

Some experimental studies have also reported beneficial effects of aspirin on erectile function. In diabetic rats, aspirin has been found to normalize the diminished mean intracavernosal pressure/mean arterial blood pressure ratio required to recuperate erectile function [16]. Argiolas et al. [3] reported that aspirin had beneficial effects on erectile function at the peripheral but not central level. 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 [6].

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 [16]. 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 [13].

This benefit of aspirin 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 [26]. 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 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 [26].

There is also indirect evidence for the beneficial effects of aspirin on erectile function from a study that assessed the effectiveness of a progressive treatment program for ED in patients with cardiovascular diseases. In this study of 453 ED patients with vascular risk factors who received anti-ED treatment, 48 patients (10.7%) achieved spontaneous erection 2 years later, of whom 46 (95.8%) were taking aspirin. No association was found between aspirin and adverse effects, with no differences were noted between patients taking or not taking aspirin [17].

Furthermore, Tauseef et al. [28] suggested that ASA with antioxidant activity ameliorated endothelium-dependent vasorelaxation because of the raised bioavailability of NO. Bornman et al. [6, 7] 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. Hafez et al. [16] also suggested that ASA might be used in the prophylactic treatment of diabetic ED to preserve the erection capacity of patients.

Interestingly, despite the experimental studies reporting positive effects of aspirin on penile erection, and more importantly, despite studies reporting the increased platelet activation in VED patients [2, 5, 10, 15, 19, 22, 27], to date, there has been no study on the effect of aspirin on VED. The antiplatelet effect of aspirin has been known for many years, and MPV, a potential marker of platelet reactivity, is used routinely in inpatient and outpatient settings at a relatively low cost [9, 19]. This is the first study to investigate the efficacy of aspirin in VED.

Minhas et al. [20] investigated the interaction of endothelium-derived NO and PGs in regulating the corporal smooth muscle tone in rabbit corpus cavernosum, and they reported

that there was a tonic release of NO which did not appear to be inhibited by a vasoconstrictor prostanoid. Endothelium-dependent relaxation to acetylcholine results in the dual production of NO and a cyclooxygenase-derived endothelium contracting factor, which acts in opposition to NO; this factor is unlikely to act on PGH2/TXA2 receptors.

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 [3]. Hafez et al. [16] 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 ASA in diabetes. They said that based on these findings, ASA 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 [16].

PGs, which seem to play a role in regulating penile erection, also interact with NO in several ways. Importantly, the release of a COX-dependent contracting factor by the corpus cavernosa, as shown by Minhas et al., can explain why aspirin improves erectile dysfunction [20, 26].

This is the first clinical study investigating the effect of aspirin in VED. Although there are some experimental studies investigating the relationship between aspirin and penile erection, there has been no clinical study on patients with VED. The present study demonstrates that aspirin may be an effective and safe therapeutic option for the treatment of VED, especially in patients with elevated MPV. The sample size in this study provided at least 95% power in detecting clinically significant treatment differences (change from baseline score between subjects, treated with aspirin 100 mg vs. placebo) in IIEF-EF, SEP-2, and SEP-3. But this study has some limitations. For example, subjects were relatively young and a highly select patient population. Many potential ED patients, including elderly men with comorbidities such as diabetes and hypertension, were not included in the study due to rather strict exclusion criteria. As a result, the number of subjects was limited and the patient population was selective. For this reason, similar studies should be performed with larger and more diverse patient groups.

Conclusions

Aspirin is an effective and safe therapeutic option for patients with VED, especially for patients with a high MPV. Low-dose aspirin may be used in patients with ED for treatment purposes or for delaying penile atherosclerosis. However, there is a need for more extensive studies on this subject.

Compliance with ethical standards

Conflict of interest Both authors declare that they have 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 Declaration of Helsinki (1964) and its later amendments or comparable ethical standards.

Human and animal rights statement 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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