

ORIGINAL PAPER

Evaluation of the effect of daily tadalafil 5 mg versus daily sildenafil 25 mg on neutrophil-lymphocyte and platelet-lymphocyte ratios in patients with erectile dysfunction: A comparative randomized controlled study

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Summary

Background: Previous studies had shown that the neutrophils/lymphocytes (NLR) and platelets/lymphocytes (PLR) ratios could be used as markers of inflammatory load as well as prognostic factors in several medical conditions. The current study aimed to compare between the effect of using daily tadalafil 5 mg/day versus daily sildenafil 25 mg/day in improving erectile function as well as their ability to reduce NLR and PLR.

Methods: One hundred and four participants were recruited. Seventy-four randomized patients with erectile dysfunction were equally divided into 2 groups. Patients in group A used daily tadalafil 5 mg for 2 months while patients in group B used daily sildenafil 25 mg for 2 months. Patients were collected from June 2022 to June 2023. Thirty healthy individuals served as controls. All patients and controls were evaluated using the validated Arabic version of the international index of erectile function (ArIIIEF-5) at baseline and after 2 months of medical treatment. Five cc of venous blood sample was obtained before and after 2 months of medical treatment to compare the effect of phosphodiesterase type 5 inhibitors (PDE-5Is) intake for erectile dysfunction on PLR and NLR before and after treatment.

Results: The current study showed that there were no statistically significant differences between the cases and the controls apart from the ArIIIEF-5 scores. Moreover, there was no significant difference between patients in group A and those in group B regarding PLR and NLR post administration of PDE-5Is.

Interestingly, patients in group A demonstrated a highly significant difference between the ArIIIEF-5 scores as well as the PLR and the NLR before and 2 months after administration of daily tadalafil 5 mg. On the other hand, patients in group B who were administered daily sildenafil 25 mg for 2 months demonstrated only a highly significant difference between the ArIIIEF-5 scores before and after administration. Meanwhile, patients in group B did not reveal any statistically significant difference in the PLR and the NLR before and 2 months after administration of sildenafil 25 mg. Further regression analysis after adjustment of different variables of the study showed a significant correlation between ArIIIEF-5 and PLR in patients who received daily tadalafil 5 mg ($r = 0.430$, $p = 0.004$).

Conclusions: Tadalafil and sildenafil have similar clinical efficacy in treating erectile dysfunction. However, tadalafil is more effective in lowering PLR and NLR compared to sildenafil.

KEY WORDS: Erectile dysfunction; neutrophils/lymphocytes (NLR); platelets/lymphocytes (PLR); tadalafil; sildenafil.

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INTRODUCTION

Erectile dysfunction (ED) is an inability to provide adequate erection to initiate or maintain any sexual activity (1). ED prevalence in adult males is approximately 20% (2). Previous studies had shown that the neutrophils/lymphocytes (NLR) and platelets/lymphocytes (PLR) ratios could be used as markers of inflammatory load as well as prognostic factors in several medical conditions (3-4). The common pathophysiological conditions underlying ED, CVD and other vascular diseases included inflammation, atherosclerosis and endothelial dysfunction (5). The NLR and PLR were known to be potential markers of inflammation in vascular diseases and inflammation play a critical role in the initiation and development of vascular endothelial dysfunction and atherosclerosis (6). Neutrophils produce and secrete several inflammatory mediators including myeloperoxidase (MPO) and reactive oxygen species (ROS) which can be responsible of myocardial and non-myocardial tissue damages (7).

Additionally, platelets release numerous inflammatory mediators that modify leukocyte and endothelial responses via different inflammatory stimuli (8).

A modern study had revealed that NLR and PLR had been proposed as biomarkers of subclinical inflammation and many studies had investigated these ratios (9). A previous study had demonstrated that onset and severity of ED had been attributed to increased levels of inflammatory biomarkers (10). In the same context, NLR and PLR were used as signs of inflammation together with a significant relationship between development of ED and these inflammatory markers (11). Previous studies reported a chronic effect of sildenafil and tadalafil on endothelial function and pro-inflammatory markers (12). Das (2007) stated that different cohorts of ED patients were associat-

ed with increased levels of inflammatory markers as well as the significant ability of oral *phosphodiesterase-5 inhibitors* (PDE-5Is) to decrease these markers (13). The current study aimed to compare between the effect of using daily tadalafil 5 mg/day versus daily sildenafil 25 mg/day in improving erectile function as well as their ability to reduce NLR and PLR.

PATIENTS AND METHODS

One hundred and four participants with *erectile dysfunction* (ED) were recruited. Seventy-four randomized patients were equally divided into 2 groups. Thirty healthy individuals served as controls. Patients in group A used daily tadalafil 5 mg for 2 months while patients in group B used daily sildenafil 25 mg for 2 months. Patients were collected from the andrology outpatient clinic, Assiut University Hospital from June 2022 to June 2023. The institutional review board approved the study (17101846) that conforms to Helsinki declaration 2013 (14). All Patients signed a written informed consent after explaining the steps and the aim of the study. They were randomized by simple numbering method.

Inclusion criteria of the patients

Any male patient aged 25 to 60 years in a stable relationship and suffering from ED was included.

Exclusion criteria of the patients

Patients who suffered from severe uncontrolled medical conditions, patients under treatment with sublingual nitrate, patients with blood diseases that affect sexual function and patients using cytotoxic drugs or immunosuppressive drugs were excluded. Also, patients without partners were excluded.

Inclusion criteria of the controls

They were age matched potent controls who attended the outpatient clinic for fertility checkup.

All participants were subjected to the following steps. Medical as well as sexual and surgical histories were obtained. General and local examinations were done. All patients and controls were evaluated using the validated *Arabic version of the international index of erectile function* (ArIIEF-5) at baseline and after 2 months of medical treatment (15). Five cc of venous blood sample was obtained before and after 2 months of medical treatment by using sterile 5 ml syringe then the sample poured into EDTA vacuum tube. Then gentle mixing was performed to obtain complete blood count using CELL-DYN haematology analyzer device to compare the effect of PDE-5Is intake for ED on PLR and NLR before and after treatment. Patients in group A received daily tadalafil 5 mg while patients in group B received daily sildenafil 25 mg for 2 months.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean,

standard deviation, median and *inter-quartile range* (IQR). Chi-square test was used for categorical variables, to compare between different groups. Student t-test was used for normally distributed quantitative variables and to compare between two studied groups. Paired t-test was used for normally distributed quantitative variables and to compare between two repeated measures. Mann-Whitney test was used for nonparametric quantitative variables and to compare between two studied groups. Wilcoxon test was used for nonparametric quantitative variables and to compare between two repeated measures. Significance of the obtained results was judged at the 5% level.

RESULTS

Table 1 showed that there were no statistically significant differences between the cases and the controls apart from the ArIIEF-5 scores. Furthermore, the current study revealed that there was no statistically significant difference between patients in group A and those in group B regarding the ArIIEF-5 prior to administration of PDE5-Is (Table 2). Also, the current study demonstrated that there were no statistically significant differences between patients in group A and those in group B regarding PLR and NLR prior to administration of PDE5-Is (Table 2). Conversely, there was no statistically significant difference between patients in group A and those in group B regarding the ArIIEF-5 after intake of PDE5-Is (Table 3).

Table 1.
Socio-demographic data of the participants.

	Tadalafil Mean SD	Sildenafil Mean SD	Controls Mean SD	P-value
Age	44.2 ± 6.9	45.7 ± 6.1	45.1 6.5	0.602
ArIIEF5 before	10.8 ± 4.7	10.2 ± 4.8	23.9 ± 0.9	0.000
PLR before	126.3 ± 36	117.3 ± 36.9	110 ± 46.9	0.206
NLR before	2.2 ± 1.17	2 ± 1.19	1.9 ± 1.4	0.686

ArIIEF5 = the validated Arabic version of the international index of erectile function; PLR = platelets/lymphocyte ratio; NLR = neutrophils/lymphocyte ratio.

Table 2.
ArIIEF-5 and NLR and PLR among studied cases before intervention.

		Group A - Tadalafil (n = 37)	Group B - Sildenafil (n = 37)	P
ArIIEF-5	Range	5-20	5-19	0.507
	Median (IQR)	9 (7-15)	8 (6-15)	
Erectile dysfunction		N	N	0.741
		%	%	
		No	No	
		Mild	Mild	
Moderate		17	14	37.8
Severe		13	16	43.2
PLR	Range	45.6-185	60-194	0.296
	Mean ± SD	126.25 ± 36.04	117.33 ± 36.91	
NLR	Range	0.48-3.9	0.56-4.3	0.384
	Median (IQR)	2.1 (1-3.2)	1.8 (0.8-3.1)	

ArIIEF5 = the validated Arabic version of the international index of erectile function; PLR = platelets/lymphocyte ratio; NLR = neutrophils/lymphocyte ratio.

Table 3. ArIIIEF-5 and NLR and PLR among studied cases post intervention.

		Group A - Tadalafil (n = 37)	Group B - Sildenafil (n = 37)	P		
ArIIIEF-5	Range	5-24	5-24	0.102		
	Median (IQR)	20 (17-22)	18 (10-22)			
Erectile dysfunction		N	%	N	%	0.323
	No	17	45.9	11	29.7	
	Mild	12	32.4	11	29.7	
	Moderate	4	10.8	7	18.9	
	Severe	4	10.8	8	21.6	
PLR	Range	31.6-148	43.8-182.5	0.197		
	Mean ± SD	99.73 ± 24	108.58 ± 33.69			
NLR	Range	0.38-3.52	0.56-4.5	0.523		
	Median (IQR)	1.1 (1-1.4)	1.1 (0.7-1.9)			

ArIIIEF5 = the validated Arabic version of the international index of erectile function; PLR = platelets/lymphocyte ratio; NLR = neutrophils/lymphocyte ratio; IQR: Interquartile range.

Table 4. ArIIIEF-5 and NLR and PLR pre and post-intervention in group A.

Group A who received tadalafil 5 mg		Pre-intervention (n = 37)		Post-intervention (n = 37)		P
ArIIIEF-5	Range	5-20		5-24		< 0.001*
	Median (IQR)	9 (7-15)		20 (17-22)		
Erectile dysfunction		N	%	N	%	< 0.001*
	No	0	0	17	45.9	
	Mild	7	18.9	12	32.4	
	Moderate	17	45.9	4	10.8	
	Severe	13	35.1	4	10.8	
PLR	Range	45.6-185		31.6-148		< 0.001*
	Mean ± SD	126.25 ± 36.04		99.73 ± 24		
NLR	Range	0.48-3.9		0.38-3.52		< 0.001*
	Median (IQR)	2.1 (1-3.2)		1.1 (1-1.4)		

ArIIIEF5 = the validated Arabic version of the international index of erectile function; PLR = platelets/lymphocyte ratio; NLR = neutrophils/lymphocyte ratio; IQR: Interquartile range.

Moreover, there was no significant difference between patients in group A and those in group B regarding PLR and NLR post administration of PDE5-Is (Table 3). Interestingly, patients in group A demonstrated a highly significant difference between the ArIIIEF-5 scores as well as the PLR and the NLR before and 2 months after administration of daily tadalafil 5 mg (Table 4).

On the other hand, patients in group B who were administered daily sildenafil 25 mg for 2 months demonstrated only a highly significant difference between the ArIIIEF-5 scores before and after administration (Table 5). Meanwhile, patients in group B did not reveal any statistically significant difference in the PLR and the NLR before and 2 months after administration of sildenafil 25 mg (Table 5).

Further regression analysis after adjustment of different variables of the study showed a significant correlation between ArIIIEF-5 and PLR in patients in group A who received daily tadalafil 5 mg ($r = 0.430$, $p = 0.004$) (Table 6). It should be mentioned that no other correlation was observed (Table 6).

Table 5. ArIIIEF-5 and PLR and NLR pre and post-intervention in group B.

Group B who received tadalafil 25 mg		Pre-intervention (n = 37)		Post-intervention (n = 37)		P
ArIIIEF-5	Range	5-19		5-24		< 0.001*
	Median (IQR)	8 (6-15)		18 (10-22)		
Erectile dysfunction		N	%	N	%	< 0.001*
	No	0	0	11	29.7	
	Mild	7	18.9	11	29.7	
	Moderate	14	37.8	7	18.9	
	Severe	16	43.2	8	21.6	
PLR	Range	60-194		43.8-182.5		0.229
	Mean ± SD	117.33 ± 36.91		108.58 ± 33.69		
NLR	Range	0.56-4.3		0.56-4.5		0.368
	Median (IQR)	1.8 (0.8-3.1)		1.1 (0.7-1.9)		

ArIIIEF5 = the validated Arabic version of the international index of erectile function; PLR = platelets/lymphocyte ratio; NLR = neutrophils/lymphocyte ratio; IQR: Interquartile range.

Table 6. PLR and NLR and smoking in both groups and tadalafil and sildenafil post intervention.

ArIIIEF-5		PLR	NLR	Smoking
Tadalafil	Pearson correlation	0.430	0.029	0.072
	P value	0.004	0.433	0.336
Sildenafil	Pearson correlation	0.168	-0.066	-0.061
	P value	0.161	0.349	0.360

ArIIIEF5 = the validated Arabic version of the international index of erectile function; PLR = platelets/lymphocyte ratio.

DISCUSSION

The current study demonstrated that baseline PLR and NLR were higher in the patients compared to the controls. However, they did not show any significant difference. Consistently, Demirci and Ozgur (2019) found that the median NLR level and PLR level were higher when compared to controls in mild-moderate ED and severe ED groups (16). Similarly, Aslan *et al.* (2019) found that NLR was higher in the patients compared to the controls (17) and that it also predicted ED and it might be helpful in diagnosing ED (17). Zhang *et al.* (2022) reported that NLR and PLR were significantly higher in ED patients compared with healthy controls (18) and Ventimiglia *et al.* (2018) determined that NLR was 3 times higher in severe ED patients and that they were independent predictors (19). A modern retrospective study conducted by Akbas *et al.* (2016) showed that the PLR value increased proportionately with the severity of ED (20). Our study did not show any statistically significant difference between the studied groups regarding PLR and NLR post-intervention. Kilic *et al.* (2023) reported that there was no significant difference in NLR or PLR between ED patients who did not respond to PDE5I treatment and controls who responded to treatment (21) and that there was a highly significant difference between ArIIIEF-5 scores before and after intervention in the studied groups who received daily tadalafil 5 mg and daily sildenafil 25 mg. Similarly, Gong *et al.* (2017) revealed that sildenafil and tadalafil had equivalent abilities to improve IIEF

scores (22). However, Rubio-Aurioles *et al.* (2012) revealed that the time concerns domain score of the *Psychological and Interpersonal Relationship Scales* (PAIRS) was significantly lower for daily tadalafil 5 mg compared with sildenafil on demand treatment (23) showing that tadalafil improves sexual confidence more efficiently than sildenafil (23).

Interestingly, our patients in group A who received daily tadalafil 5 mg for 2 months showed a high statistically significant difference between pre and post-intervention PLR and NLR. Meanwhile, patients in group B who received daily sildenafil 25 mg for 2 months did not show any statistically significant difference between pre and post-intervention PLR and NLR. Consistently, La Vignera *et al.* (2014) showed that tadalafil has a preventive effect on both endothelial apoptosis and excessive platelet adhesion in ED patients (24). Furthermore, a recent Egyptian study demonstrated that daily tadalafil 5 mg supplementation lowers these markers with significant improvement in the erectile function (25). The superiority of tadalafil versus sildenafil in lowering PLR and NLR in the current study might be explained by the shorter half-life of sildenafil but no available data support this hypothesis that needs further investigations.

Although tadalafil and sildenafil showed significant improvement in improving the ArIIIEF-5 scores, yet, tadalafil was superior to sildenafil in lowering the studied inflammatory markers. A previous systematic review conducted by Mirone *et al.* (2008) stated that tadalafil was preferred by the patients compared to sildenafil for several reasons (26). Firstly, patients preferred tadalafil owing to its flexibility (27). Secondly, tadalafil was also preferred owing to its better tolerance (28). Finally, tadalafil was preferred by the patients for its higher efficacy (28-29). To the best of our knowledge, the current study is one of the first to demonstrate higher efficacy of tadalafil compared to sildenafil in lowering NLR and PLR. However, there were several limitations of the current study that should be acknowledged. The sample size was relatively small and the patients were followed up for short duration.

CONCLUSIONS

Tadalafil and sildenafil have similar clinical efficacy in treating ED. However, tadalafil is more effective in lowering PLR and NLR compared to sildenafil. Future studies are required to replicate this finding as it may add superiority to tadalafil compared to sildenafil.

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Conflict of interest: The authors declare no potential conflict of interest.