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THE EFFECT OF HALF-LIFE & SELECTIVITY OF PDE-5 INHIBITERS ON BLOOD HOMEOSTASIS

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ABSTRACT

Elevation of erectile dysfunction percentage with increasing age and existing of different disease such as diabetes mellitus, depression, hypercholesterolemia, ischemic cardiac disease, hypertension and obesity. Develops in clinical research in ED through previous15 years, resulted in advance of several modern treatment options, including pharmacological agents for intraurethral, intracavernousal, also recently, oral Phosphodiesterase type-5 inhibitors (PDE5-i). A phosphodiesterase type 5 inhibitor (PDE5 inhibitor): Sildenafil, tadalafil, vardenafil, and the newer types are selectively inhibit PDE5, is a drug used to block the degenradative action of cGMP-specific phosphodiesterase type 5 (PDE5) on cyclic GMP in the smooth muscle cells lining the blood vessels supplying the corpus cavernosum of the penis. This study is aimed to investigate the effect of half-life and PDE-5 selectivity on biochemical changes that occur during administration of PDE-5 inhibitors (Sildanafile or Tadalafile) on some hematological parameters especially Bleeding Time (IVY), fibrinogen weight, D-dimer and its titer as compared to the control. This study included seventy male patients with erectile dysfunction. In addition to 70 control subjects .All the participants were with range of age (20-50 years) and apparently had no other diseases .Thirty- eight subjects with erectile dysfunction ED were treated with Sildenafile tablet of 100 mg., and thirty-two subjects with ED treated with Tadalafile tablet of 20 mg. Venous blood specimens were utilized to perform hematological analysis. Results revealed that Sildenafil produced significant alterations in Bleeding Time (IVY), fibrinogen weight, D-Dimer values and its titer after 6 weeks of starting treatment. Whereas, tadalafil produced more pronounced alterations after 4 weeks of treatment on the same parameters. As conclusions; PDE-5 inhibitors (silenafil & tadalafil) enhance coagulation mechanism and thrombus formation. Sildenafil have less effects because of

shorter half-life and low selectivity than that produced by tadalafil when used for the same duration of time.

KEYWARDS: PDE-5 inhibitors, Sildenafil, Tadalafil, Bleeding Time (IVY), Fibrinogen, D-dimer, Titer of D-dimer.

INTRODUCTION

Erectile dysfunction (ED) is continuous impotence to perform erection to adequate level for sexual performance.[1] The probability of erectile dysfunction increases with ageing[2] and the presence one or more of this conditions: diabetes mellitus[3], hypertension,[4] hypercholesterolemia,[5] ischemic cardiac disease,[6] depression[7] and obesity.[8] In spite of cigarette smoking it may increase the risk of presenting with peripheral vascular disease and hypertension, but it is not a direct causative factor.[9] Drugs and alcohol abuse may also increase the risk of erectile dysfunction.[10] More than 70% of the male population affected by moderate to severe erectile dysfunction is complaining of concomitant diseases.[11] The probability of manifested severe erectile dysfunction increases two-fold in the presence of the above mentioned diseases,[12] thus modification of associated risk factors may contribute to improve erectile dysfunction in internal medicine patients.[13] Phosphodiesterase type-5 inhibitors (PDE5-inhibiters) today are used in treatment of male erectile dysfunction.[14] Sildenafil, vardenafil and tadalafil all inhibit PDE5 at the level of the corpus cavernosum with different onset of action.[15]

A phosphodiesterase inhibitor is a drug that blocks one or more of the subtypes of the enzyme phosphodiesterase (PDE),(15) thereby preventing the inactivation of the intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) by the respective PDE subtype(s).[16] PDE5 selective inhibitors: Sildenafil, tadalafil, vardenafil, and the newer types are selectively inhibit PDE5, which is cGMP-specific and responsible for the degradation of cGMP in the corpus cavernosum. These phosphodiesterase inhibitors are used primarily as remedies for erectile dysfunction, as well as having some other medical applications such as treatment of pulmonary hypertension.[17,18] But growing evidence supports important roles for the enzyme in both the vasculature and heart in disorders such as cardiac failure. PDE-5A up regulation may contribute to a decline in cGMP and protein kinase G signaling, exacerbating dysfunction. PDE5A plays an important role in the pulmonary vasculature where its inhibition benefits patients with pulmonary hypertension. In the heart, PDE5A signaling appears compartmentalized, and its inhibition is

cardioprotective against ischemia-reperfusion and antracycline toxicity, blunts acute adrenergic contractile stimulation, and can suppress chronic hypertrophy and dysfunction attributable to pressure-overload.[19,20] Phosphodiesterase type-5 inhibitor (PDE5-i) drugs were first marketed in 1998 (sildenafil) for 'on-demand' treatment of male erectile dysfunction (ED) of any origin.[21] They selectively inhibit intrapenile PDE5 isoenzyme which in turn increases intracellular cyclic guanosine monophosphate levels, thus resulting in prolonged relaxation of cavernosum smooth muscle cells and facilitating the erection process(14).Since 2003, two new molecules (tadalafil and vardenafil) have been introduced, resulting in greater interest in these compounds and leading patients to ask for more prescriptions from their doctors. The vast use of PDE5-i in diabetic and cardiovascular ED patients led researchers to investigate their possible extra sexual effects.[22]

This study is aimed to investigate the biochemical changes associated with administration of PDE-5 inhibitors (Sildanafile or Tadalafile) in relation to half-life and PDE5 selectivity of drug on some hematological parameters: bleeding time (IVY), fibrinogen weight, D-dimer and its titer, compared to the controls.

MATERIAL & METHODS

Patients Selection

This study included seventy out patients (all of them are males) from Baghdad city, where the samples were collected and brought to the laboratory in the Hematology Center of Al-Mustansyria University for period from the first of February/ 2014 to the end of April/ 2014.In addition to 70 control subjects .All the participants were with range of age (20-50 years) and apparently had no other diseases. All participants were well informed about the study and gave their consent to participate prior to having blood samples taken .Those subjects were divided into three groups:

1. **Group C**: composed of seventy subjects as a control (mean age 35.257±7.692 yrs).
2. **Group S**: included thirty- eight subjects with erectile dysfunction ED (mean of age39.710 ± 6.559 yrs) those intake Sildenafil tablet of 100 mg.
3. **Group T:** included thirty-two subjects with ED (mean of age 29.968±5.214 yrs) those intake Tadalafil tablet of 20 mg.

The subjects in the groups S&T started taking the drug two tablets weekly for four weeks and then one tablet daily for the next four weeks. Table (1) summarizes demographic data of subjects included in the study.

Specimen Analysis

Venous blood specimens were withdrawn from each subject initially 2 ml of the specimen was placed into EDTA tube for complete blood count performance.[23,24] When the results were normal (especially the platelet count),[25] then another specimen was withdrawn 1.8 ml of blood was placed in plane tube contain 0.2 ml (3.2%) sodium citrate to determine the Quantitative Determination of Fibrinogen(FIB), and Latex Agglutination Slide Test for the Qualitative and Semi-Quantitative Determination of D-dimer.

(Table -1) Demographic Data of Subjects

Characters/Groups	Group C N=70	Group S N=38	Group T N=32	P
Gender* Female Male	 0 (0%) 70 (100%)	 0 (0%) 38 (100%)	 0 (0%) 32 (100%)	
Residence Village City	 0 (0%) 70 (100%)	 0 (0%) 38 (100%)	 0 (0%) 32 (100%)	
Smoking habit Smoker Non-smoker	 0 (0%) 70 (100%)	 0 (0%) 38 (100%)	 0 (0%) 32 (100%)	
Age (Mean ± SD)	35.257±7.692	39.710±6.559	29.968±5.214	P≤0.05
Body Mass Index (Mean ± SD)	26.900±2.11	27.122±1.633	26.83±3.990	

RESULTS

1. IVY Values

Table (2) show that both S group &T group were not-significantly differs from each other before treatment and from control group. Treatment with Sildenafil after 4 weeks decrease the IVY values by (24.47%) and continue to decrease after 6 weeks and 8 weeks of treatment by (32.96% & 34.2% respectively) from the baseline ,but IVY value after 8 weeks of sildenafil treatment was not-significantly deference from the value after 6 weeks of treatment. While tadalafil treatment after 4 weeks(T2) was significantly lowering from the baseline by (36.2%) and highly decrease after 6 weeks (T3) by (51.24%) from the baseline. after 8 weeks of treatment(T4) was significantly deference from (T3) that increase by (21.59%),but (T4) not-significantly deference from (T2) because it decrease only by (6.95%). All above changes and deference between S group & T group at the same period shown in figure (1).

Table (2): IVY Values For All Groups At Different Periods Of Treatment

Groups / Parameter	C	S1	T1	S2	T2	S3	T3	S4	T4	P
IVY (min)	7.20± 0.23 A	7.19± 0.23 A	7.22 ±0.25 A	5.43 ±0.37 B	4.60 ±0.41 C	4.82 ±0.36 C	3.52 ±0.41 D	4.73± 0.38 C	4.28 ±0.51 C	**≤0.05**

C : control group of 70 subjects.T1 : T group before therapy.T2 : T group after 4 weeks of therapy(2 dose weekly of 20 mg Tadalafil) .T3 : T group after 6 weeks of therapy (single dose daily of 20 mg Tadalafil).T4 : T group after 8 weeks of therapy(single dose daily of 20 mg Tadalafil).S1 : S group before treatment . S2 : S group after 4 weeks of therapy(2 dose weekly of 100 mg of sildenafil) .S3 : S group after 6 weeks of therapy (single dose daily of 100 mg of sildenafil) .S4 : S group after 8 weeks of therapy(single dose daily of 100 mg of sildenafil). P: probability. Mean values with the same letter are not significantly different. Means with the different letter are significantly different.

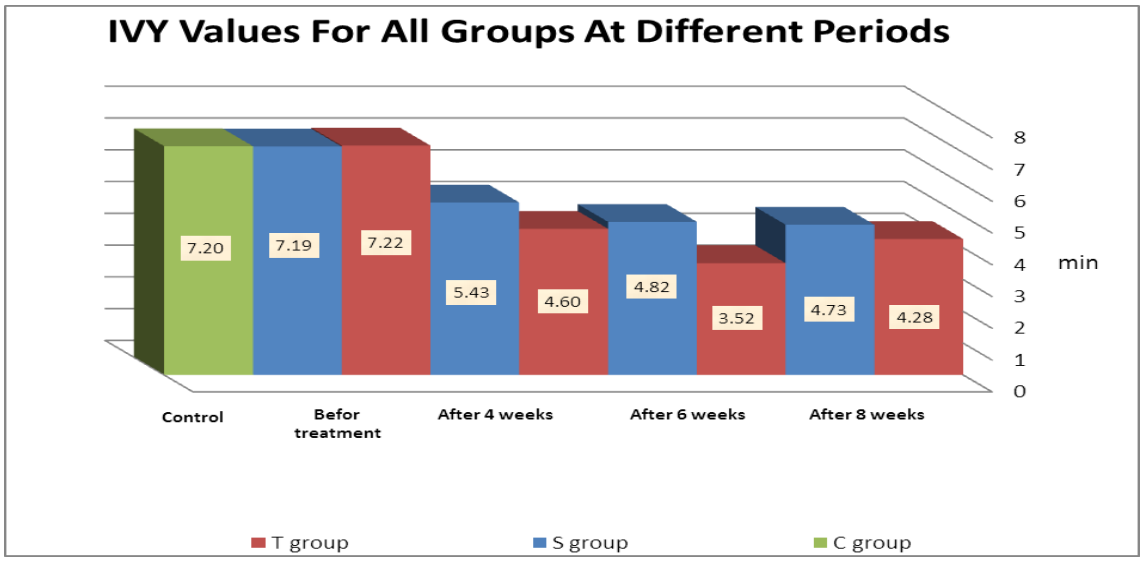

Figure (1): IVY Values For All Groups At Different Periods Of Treatment.

2. Fibrinogen Weight (FIB.)

Treatment with sildenafil produced no significant change throughout the study period (8 weeks) as presented in Table (3) .Whereas Tadalafil treatment caused significant elevation in fibrinogen values after 4 weeks (by 20.7 %) ,but decreased after (8 weeks) of Tadalafil therapy (by 42.6 %) as shown in figure (2).

Table (3): Fibrinogen For All Groups At Different Periods Of Treatment.

Groups / Parameter	C	S1	T1	S2	T2	S3	T3	S4	T4	P
FIB. (g\l)	2.91 ±0.8 B	2.99 ±0.11 B	2.79 ±0.18 B	2.99± 0.11 B	3.37 ±0.14 A	2.97 ±0.08 B	3.36 ±0.11 A	2.92 ±0.11 B	1.60 ±0.12 C	**≤0.05**

C : control group of 70 subjects.T1 : T group before therapy.T2 : T group after 4 weeks of therapy(2 dose weekly of 20 mg Tadalafil) .T3 : T group after 6 weeks of therapy (single dose daily of 20 mg Tadalafil).T4 : T group after 8 weeks of therapy(single dose daily of 20 mg Tadalafil).S1 : S group before treatment . S2 : S group after 4 weeks of therapy(2 dose weekly of 100 mg of sildenafil) .S3 : S group after 6 weeks of therapy (single dose daily of 100 mg of sildenafil) .S4 : S group after 8 weeks of therapy(single dose daily of 100 mg of sildenafil). P: probability. Mean values with the same letter are not significantly different. Means with the different letter are significantly different.

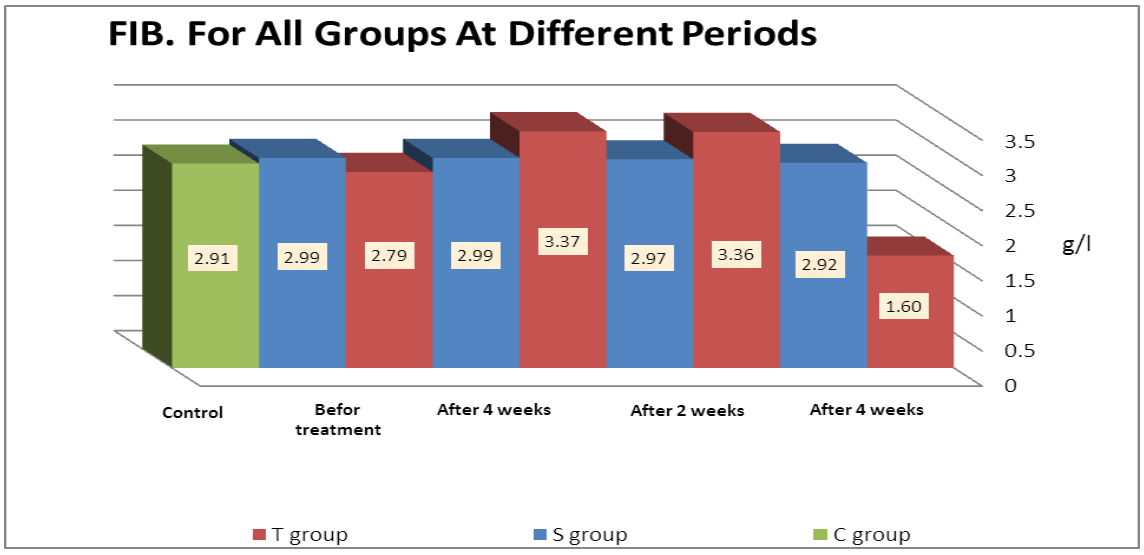

Figure (2): Fibrinogen For All Groups At Different Periods Of Treatment.

3. Titer of D-dimer

Table (4) show the baseline of Tadalafil treatment was significantly difference from the control and baseline (P≤0.05) of sildenafil treatment. Sildenafile after 4 weeks was no significantly difference ,but the treatment was significantly difference after 6 weeks & 8 weeks by sildenafil from the baseline (by 40% &67.5% respectively), but they were not-significantly difference from each other.

Tadalafil treatment after 4 weeks produced significant elevation in D-dimer titer from the baseline (P≤0.05) that increased by (80%), and continue to increase after 6 weeks and 8 weeks by (200% & 210% respectively).

Furthermore, Sildenafil treatment resulted in lower values of D-dimer titer as compared to Tadalafil treatment of the same periods as shown in figure (3).

Table (4): Titer Of D-Dimer For All Groups At Different Periods Of Treatment.

Groups / Parameter	C	S1	T1	S2	T2	S3	T3	S4	T4	P
Titer**(FEU)**	0.40 ±0.0 D	0.41±0. 0 D	0.5 ±0.1 C	0.46± 0.04 D	0.9 ±0.14 B	0.56± 0.10 C	1.50± 0.23 A	0.67± 0.13 C	1.55± 0.22 A	**≤0.05**

C : control group of 70 subjects.T1 : T group before therapy.T2 : T group after 4 weeks of therapy(2 dose weekly of 20 mg Tadalafil) .T3 : T group after 6 weeks of therapy (single dose daily of 20 mg Tadalafil).T4 : T group after 8 weeks of therapy(single dose daily of 20 mg Tadalafil).S1 : S group before treatment . S2 : S group after 4 weeks of therapy(2 dose weekly of 100 mg of sildenafil) .S3 : S group after 6 weeks of therapy (single dose daily of 100 mg of sildenafil) .S4 : S group after 8 weeks of therapy(single dose daily of 100 mg of sildenafil). P: probability. Mean values with the same letter are not significantly different. Means with the different letter are significantly different.

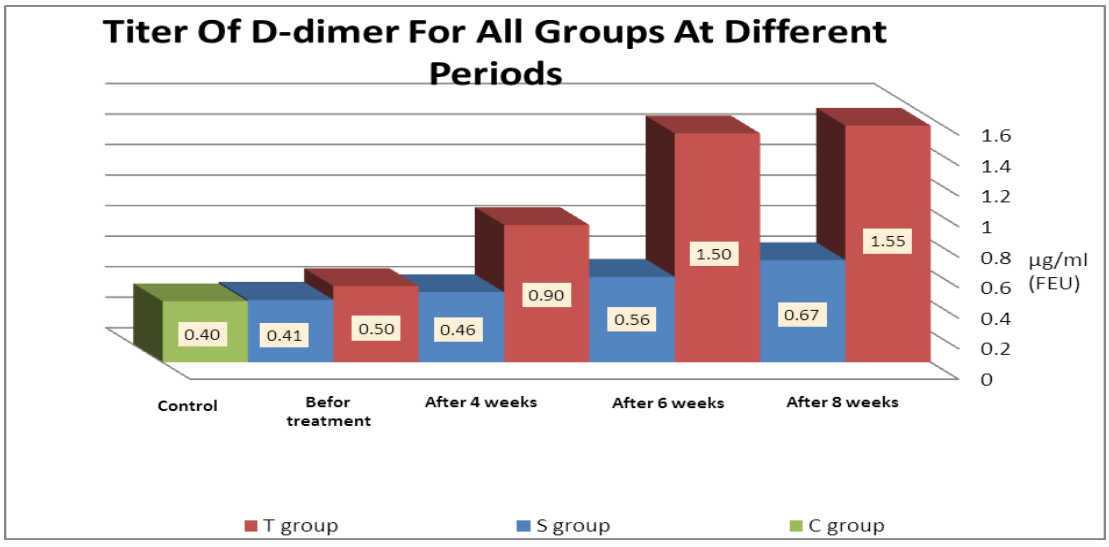

Figure (3): Titer Of D-Dimer For All Groups At Different Periods Of Treatment.

4. Daily Test of D-Dimer And Its Titer For S Group After Stop The Treatment

Table (5) showed 4 patients only that had positive values of D-dimer test and its titer directly after ended the period of treatment with sildenafil. Those patients had individual variation in tolerance this effect. Some of them continue for 2 days and the others for 4 days with different strength of this test.

TABLE (5): Daily Test Of D-Dimer And Its Titer For S Group After Stop The Treatment.

No	1st day		2nd day		3rd day		4th day		5th day		6th day		7th day	
	D-dimer	titer	D-dimer	titer	D-dimer	titer	D-dimer	titer	D-dimer	titer	D-dimer	titer	D-dimer	titer
6	+ ve	1/8	+ ve	1/4	+ ve	1/2	- ve							
10	+ ve	1/8	+ ve	1/8	+ ve	1/4	+ ve	1/2	- ve					
13	+ ve	1/8	+ ve	1/8	+ ve	1/4	-ve							
38	+ ve	1/4	+ ve	1/2	− ve									

5. Daily Test Of D-Dimer And Its Titer For T Group After Stop The Treatment.

Table (6) showed 16 patients which had positive values of D-dimer test and its titer directly after the ended the period of treatment with tdalafil. Those patients had individual variation in tolerance this effect .Some of them continues for 3 days and the other for 9 days with different strength of this test.

TABLE (6): Daily Test Of D-Dimer And Its Titer For T Group After Stop The Treatment.

No	1st day		2nd day		3rd day		4th day		5th day		6th day		7th day		8th day		9th day	
	D-dimer	titer	D-dimer	titer	D-dimer	titer	D-dimer	titer	D-dimer	titer	D-dimer	titer	D-dimer	titer	D-dimer	titer	D-dimer	titer
1	+ ve	1/8	+ ve	1/4	+ ve	1/2	+ ve	1/2	− ve									
2	+ ve	1/8	+ ve	1/4	+ ve	1/2	+ ve	1/2	− ve									
3	+ ve	1/8	+ ve	1/8	+ ve	1/4	+ ve	1/4	+ ve	1/2	+ ve	1/2	+ve	1/2	-ve			
4	+ ve	1/8	+ ve	1/4	+ve	1/2	+ve	1/2	-ve									
7	+ ve	1/8	+ ve	1/8	+ ve	1/8	+ ve	1/4	+ve	1/4	-ve							
8	+ ve	1/8	+ ve	1/8	+ ve	1/8	+ ve	1/4	+ ve	1/4	+ve	1/2	+ve	1/2	+ve	**1/2**	**-ve**	
9	+ ve	1/2	+ ve	1/2	-ve													
11	+ ve	1/8	+ ve	1/4	+ve	1/4	-ve											
12	+ ve	1/8	+ ve	1/8	+ ve	1/8	+ve	1/4	+ ve	1/4	+ve	1/2	+ve	1/2	-ve			
15	+ ve	1/8	+ ve	1/4	+ ve	1/4	+ve	1/2	+ve	1/2	-ve							
16	+ ve	1/4	+ ve	1/2	+ ve	1/2	− ve											
17	+ ve	1/8	+ ve	1/2	− ve													
23	+ ve	1/8	+ ve	1/4	+ ve	1/4	+ve	1/2	+ ve	1/2	+ve	1/2	-ve					
26	+ ve	1/8	+ ve	1/8	+ ve	1/2	+ ve	1/2	+ve	1/2	-ve							
27	+ ve	1/8	+ ve	1/4	+ ve	1/4	+ ve	1/2	− ve									
28	+ ve	1/4	+ ve	1/4	+ ve	1/2	− ve											

DISCUSSION

1. Effect Of Sildenafil And Tadalafl Treatment On Bleeding Time (IVY Method)

In spite of the continued decreased in the IVY values of both groups but it still within normal references (2-11).[26] Although the bleeding time is determined by many physiologic factors, including skin resistance, vascular tone and integrity, and platelet adhesion and aggregation . Thus, an intrinsic platelet function defect, vascular anomaly, or medications may affect platelet function and hence bleeding time value.[26-29] Table (2) showed slightly decline of IVY values in different periods of S-group as compared to the control.

As shown in figure (1), although of continuous decreasing of these values as compare to the control, but the lowering that produced by tadalafil was more obvious than that of seldinafil treatment at the same period. In spite of decline in the results of this test, but it is still within the normal references (2-11).[26] Such decline could be related to the thrombogenic effect of the sildenafil due to its effect on platelet activity by decreasing cGMP.[30] While in T-group the values start to decrease slightly till T3 period and suddenly increase in T4 period. These sudden increment may as a result to consumption fibrinogen due to fibrinolysis and coagulation mechanism[31,32] because of strong coagulating effect of more selective PDE-5 inhibitor tadalafil; low selectivity of sildenafil for PDE5 (with a K_m of about 1 μm) where it inhibited both PDE-5 &PDE-2.[33,34,35] By inhibition of PDE-5 lead to increase cGMP that will stimulate PDE-2[36,30] that will inhibition by low selective effect of sildenafil [260] leading to increase both cAMP &cGMP,[37,38] but cGMP will activate PDE-5 that will hydrolysis cGMP by feedback mechanism, and cAMP elevation will decreased platelet activity.[30,37,38] While the more selective PDE5 tadalafil (K_D range of 0.9–6.7 nm; 200–700 times more selective for PDE5),[40] Inhibit PDE-5 only leading to increased the intra-platelet cGMP that cause stimulation of PDE-2,[36] leading to hydrolysis both cAMP and cGMP and stimulate platelet activity.[41]

2. The Effect Of Sildenafil And Tadalafil Treatment On Fibrinogen Weight (FIB.)

Fibrinogen is a essential protein contribute in the homeostasis process produce by the liver about (3-5) g/l daily increase this value or decrease mean there is a defect,[42,43] elevated the value mean increase the production of fibrinogen as reflex for it's consumption ,and low value of fibrinogen mean either decrease production of fibrinogen because liver diseases or very sever consumption of fibrinogen because some diseases or conditions like thrombus formation that stimulated fibrinolysis mechanism.[44,45]

Table (3) shown continuous decreased values for fibrinogen weight at different periods in S-group where all values within the normal range (2-4).[46] While fibrinogen weight at different periods for T-group was:T1 period ;the base line where before beginning of the study and during the irregularity of treatment within the normal range ,but after two dose weekly the values of fibrinogen weight ware elevated because increased the production as a reflex for increased consumption by fibrinolysis mechanism, An increased levels of fibrinogen can be found in cases of diabetes, inflammatory syndrome and obesity.[46] Furthermore, fibrinogen seems to be involved in the pathogenicity of thrombotic cardiovascular events.[47,46] Because fibrinogen can be degraded by plasmin also not fibrin only,[44] at T3 & T4 decreased the values of fibrinogen because the consumption more than production,[31,32] that mean firstly increase the thrombogenic effect of tadalafil in T1 &T2 led to increased production of fibrinogen by liver and then increase the consumption by fibrinolysis led to decrease fibrinogen values.

Regular decline in fibrinogen weight in the different periods of S-group but remind with normal reference because the consumption less than production due to low severity of fibrinolysis to thrombogensis effect of sildenafil even in daily dose. To clear why the thrombogenic effect of tadalafil more than that of sildenafil, can by the following:
Low selectivity of sildenafil for PDE5 (with a K_m of about 1 µm)[35] where it inhibited both PDE-5 &PDE-2.[33,34] When it inhibited PDE-5 leading to increase cGMP that will stimulate PDE-2[36,30] that will inhibition by low selective effect of sildenafil[39] leading to increase both cAMP &cGMP.[37,38] cGMP will activate PDE-5 but cAMP will decreased platelet activity[30,37,38] but for less degree than when which be together with cGMP. While the more selective PDE5 tadalafil (K_D range of 0.9–6.7 nm; 200–700 times more selective for PDE5),[40] inhibit PDE-5 only leading to increased the intra-platelet cGMP that cause stimulation of PDE-2,[36] resulting in hydrolysis both cAMP and cGMP together as a result sever stimulation for platelet activity.[41]

3. Effect The Treatment With Sildenafil And Tadalafl On Titer of D-dimer

After breakdown of fibrinogen molecules into fragments, the fibrin monomers that are produced, aggregate to form fibrin, which is stabilized by factor XIIIa.[47] Which represent the origin of D-dimer, the degradation product that is specific of fibrin.[48]

The values of D-dimer titer it is for the positive results only (the positive results occur when the value was more than or equal to 0.5 µg/ml,[49,50,51] while the negative results don't have any value (-ve only), but for statistical necessity considered the negative result any value smaller than 0.5 µg/ml like 0.4 µg/ml.

Table (4) showed that the control value of 0.4 µg/ml that mean all subjects were of negative values, while S1value(base line value of S-group) was 0.41 µg/ml that mean there are some subjects have positive values before started the treatment of present study that lead to elevated S1 value by 0.01 .Whereas T1 value(base line value of T-group) was 0.5 µg/ml that mean higher number of subjects were having positive values ; the number of subjects of positive values among the users of tadalafil was more than those uses sildenafil.

Since this test reflects the specific degradation of fibrin (i.e., fibrinolysis) which is the reactive mechanism responding to the formation of fibrin,[32] and D-dimer it is the final products in the hydrolysis process of fibrin.[52] Its appearance in the plasma compartment is thus proof that the fibrinolytic system is in action in response to coagulation activation.[53]

Rapid increased in the values of D-dimer titer in different periods of both groups as compared to the control and base line values (S1 & T1), mean these drugs increased coagulation mechanism as indicated by stimulating fibrinolytic mechanism, and its exist in the plasma compartment indication that fibrinolytic system is in action in response to coagulation activation.[53] That was activated because of increased fibrin presence due to thrombotic events induced by these drugs (sildenafil and tadalafil) that may occur by a mechanism of indirectly decreasing the intra-platelet cGMP because of inhibiting of PDE-5 leading to increased cGMP that re-activated PDE-5 as feedback mechanism .By compared the different periods of both group (S&T) with each other see that increased in the D-dimer titer values of T-group it very high if it is compared with previous period of the same group or with corresponding period of S-group may reach in some cases to a double or triple values as in comparing T4 by T1 which reach approximately (≈ 300%) .While these high differences can't be seen in the S-group at different periods where the difference between S1& S4 was only 61% of baseline value.

When the fibrinolytic system is activated and therefore the D-dimer level increases, hence D-dimer assays can help in the diagnosis of DIC[54].As well as, because of level of D-dimer increased during the activation states of coagulation because such states induce the

production of thrombin which is followed by the formation of fibrin and leads to fibrinolysis, and thus increases D-dimer following coagulation activation.[55]

Low selectivity of sildenafil for PDE5 (with a K_m of about 1 µm) where it inhibited both PDE-5 & PDE-2.[33,34,35] By inhibition of PDE-5 lead to increase the intra-platelet cGMP level that will stimulate PDE-2,[36] but this enzyme will inhibited again by low selective agent sildenafil[35] this will leading to increase both cAMP &cGMP.[37,38] cGMP will activate PDE-5 but cAMP will decreased platelet activity even when cGMP re-inhibition.[30,37,38] While the more selective PDE5 tadalafil (K_D range of 0.9–6.7 nm; 200–700 times more selective for PDE5),[40] Inhibit PDE-5 only leading to increased the intra-platelet cGMP firstly, and then cause stimulation of PDE-2,[36] leading to hydrolysis both cAMP and cGMP and stimulate platelet activity[41] secondly.

4. Daily Test Of D-dimer For S Group After Stopping The Treatment

Table (5) showed that 4 patients only that had positive values of D-dimer titer test at the end of period of treatment with sildenafil. Those patients had individual variation in how long these values stay positive .Some of them continue for 2 days and the other for 4 days with different strength of this test (titer). That mean continues adverse effect of sildenafil even when interrupted the treatment by these drug in spite of the short half life of sildenafil 3.7 h[56] may be because of chronic activation of platelet.[57] Because this short half life, maximum period of adverse effect was 4 days.

5. Daily Test Of D-dimer And Its Titer For T Group After Stop The Treatment

Table (6) showed 16 patients that had positive values of D-dimer titer test at the end of period of treatment with tdalafil. Individual variation in how long remain these values positive. Some of them continue for 3 days and the other for 8 days with different strength of this test (titer). That mean continues adverse effect of tadalafil even when interrupted the therapy by this drug for period longer than of sildanafil because of the long half life of tadalafil 17.5 h.[58] That mean sever effect of long half life of tadalafil on persist adverse effect due to continues effect of these agent on platelet function.

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