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EFFICACY AND SIDE EFFECTS OF SILDENAFIL CITRATE IN PATIENTS ON CHRONIC HAEMODIALYSIS WITH ERECTILE DYSFUNCTION

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ABSTRACT

Introduction: Medical Erectile dysfunction is the inability to achieve or maintain an erection for a satisfactory sexual performance. **Objective:** The objective of this study was to find the efficacy and frequency of side effects of sildenafil citrate in patients on chronic hemodialysis with erectile dysfunction (E.D). **Methods:** This study was involved 165 patients of renal failure on hemodialysis for at least six months presenting with erectile dysfunction. Sildenafil citrate (50 mg) tablet were converted into powder form and filled it in capsules. All patients received a sealed box containing the capsules. one capsule containing sildenafil citrate (50 mg) was given to all patients twice a week and advised them to take these capsules one hour before the intercourse and continue this treatment for two weeks. **Results:** Erectile dysfunction improved in 145 (87.9%) patients. There was no significant difference in the frequency of efficacy across age (p=0.496), duration of renal failure (p=0.901) and baseline IIEF (p=0.543) groups. Headache was the most frequent side effect and was reported by 27 (16.4%) patients followed by flushing (n=21, 12.7%), blurring of vision (n=9, 5.5%) and dyspepsia (n=7, 4.2%). **Conclusion:** The efficacy of sildenafil citrate was found to be 87.9% in patients of renal failure on hemodialysis presenting with erectile dysfunction. This efficacy was unaffected by patients' age, duration of renal failure and baseline IIEF score.

KEY WORDS: Renal Failure, Hemodialysis, Erectile Dysfunction, Sildinafil Citrate.

INTRODUCTION

Medical Erectile dysfunction is the inability to achieve or maintain an erection for a satisfactory sexual performance. Advanced chronic kidney disease (CKD) is associated with erectile dysfunction (ED) in males.[1] The incidence of erectile dysfunction is estimated to be between 50 to 70% depending on the stage of renal failure.[2] Sexual dysfunction in patients with chronic kidney disease comprises both physiological (Hormonal, vascular, neurological) and psychological factors.[3,4]

The erectile dysfunction (E.D) improves after successful kidney transplantation to some extent.[2,3] Dialysis improves most symptoms of end stage renal disease (ESRD), yet many patients continue to experience erectile dysfunction (ED) during the dialysis treatment. Different drugs have been used to treat erectile dysfunction in patients with chronic kidney disease like Yohimbine, Delequamine, Trazodone, Red Korean Ginseng, Limaprost, Phentolamine in ancient times but all of these drugs have unknown mechanism of action and less safety and efficacy.[5,6]

The International Index of Erectile Function (IIEF) score was introduced to assess erectile dysfunction and treatment response in 1996 for the first time.[7,8] The self-administered IIEF comprises a validated questionnaire of 15-questions. The IIEF (International Index of Erectile Function) allows its identification and its stratification into several grades according to the score obtained. The erectile function domains include: absence of ED (score>25.), mild ED (score 16- 20), moderate ED (scorell-15) and severe ED (score 5-10).

According to one study, there is a weak correlation between erectile dysfunction and duration of dialysis (p=0.073) and many studies have shown a significant relationship between sildenafil usage and improvement in erectile function (p<0.0001).[7] Placebo can improve the erectile function psychologically in some patients. However according to another comparative study, sildenafil has a more significant effect than placebo in increasing HEF score among haemodialysis patients and it has proved to be safe. In another study conducted by Ivan et al. fifty patients were taken by randomized control trial and they are given placebo and sildenafil by

double blind method, improvement was observed in 76 percent of Sildenafil patients compared to 12 percent of placebo patients according to HEF score. Sildenafil use resulted in normal erectile function score in 36 percent Sildenafil patients and p value was significant (p <0.0001). In another study conducted by Turk et al in 2002, twenty HD patients with ED were observed for sildenafil effect and the response rate was 60%. In another study by Bellovich et al. 25 HD patients were studied to see the effect of sildenafil in a placebo controlled 3- way cross over fashion and the significant efficacy was observed and there were no complications with sildenafil use. Hence, improvement was achieved in 60 to 76% of Sildenafil patients and 10 to 15% in placebo group.[2,9]

Multiple studies carried out by Siebel et al in Indian Journal of Nephrology, Sahin York et al in hemodialysis and transplant unit New York, Aslan D et al at hemodialysis Unit in Egypt, suggest good tolerability of hemodialysis (HD) patients to sildenafil citrate.[2] In one study by Ivan et al, twenty patients were observed for adverse effects. Minimum adverse effects were reported in both groups. Two patients reported moderate and severe headaches and one patient reported mild facial flushing in placebo group. In the Sildenafil group, moderate flushing and dyspepsia were reported in one patient, mild headache and dyspepsia by one patient and mild headache by one patient. In viewing above mentioned adverse effects, we will measure these variables according to frequency of adverse effects and assess safety profile. Headache, flushing and dyspepsia are the most common adverse effects in non- uremic patients.[10] In multiple studies mentioned above very few side effects were reported in either group and headaches were more intense in placebo group. Most common adverse effects according to their percentage are headache (20%), flushing (16%), dyspepsia (10%), palpitation (8%) and blurring vision (4%). Dyspepsia only occurred in sildenafil group.[10,11] In conclusion, oral sildenafil is an effective and safe treatment for ED in the patients with chronic renal failure on HD.

There are few studies on the use of Sildenafil citrate in HD patients; most of them are without frequency of side effects. As far as we know, there are few studies with Sildenafil citrate in HD patients internationally. Due to lack of local data and research on this topic, there is a significant need to Study the effect of sildenafil citrate in Pakistani male hemodialysis patients that is why we have planned this study in a population group for the first time. After approval of that study, we will be able to use sildenafil citrate safely in male patients of chronic hemodialysis to treat their erectile dysfunction and they can enjoy their lives just like normal men.

MATERIALS AND METHODS

Study Design and sample size

It's a descriptive case series. Research was conducted at Department of Urology, Services Hospital, Lahore, Pakistan. Duration of study was 6 months. The study protocol was approved by the institutional Review Board of Services Institute of Medical Sciences, Lahore, Pakistan. Sample size of 165 cases was calculated with 95% confidence level and 3% margin of error while taking expected percentage of blurring of vision to be 4% least among all side effect of sildenafil citrate in patients on chronic hemodialysis with erectile dysfunction.[10] Patients were selected by Non-Probability, Consecutive Sampling.

Inclusion Criteria

Persons having a stable relationship with a female sexual partner. Patients who were on hemodialysis (HD) for at-least 06 months undergoing mean dialysis duration of 08 hours per week with Helixone membranes. Patients with an IIEF score lower than 20. Male patients having an age range of 40-60 years.

Exclusion Criteria

Patients with penile anatomical abnormalities. Patients with severe anemia (Hemoglobin <8 mg/dl). Patients on nitrate treatment or with a history of recent (previous 6 months) stroke or myocardial infarction.

Data collection procedure

All patients were selected from hemodialysis Unit of Urology Department of Services Hospital Lahore. An informed consent was taken. A descriptive case series study was conducted. The study was approved by the Review board committee of Medical Sciences. The patients were informed sufficiently about how to use tablets, the probable complications, the symptoms of improvement, and also about international index of erectile function (IIEF) questionnaire.

Baseline IIEF was calculated for all patients. We converted the Sildenafil citrate (50mg) tablet into powder form and filled it in capsules. All patients received a sealed box containing the capsules. We delivered one capsule containing sildenafil citrate (50mg) to all patients twice a week and advised them to take these capsules one hour before the intercourse and continue this treatment for two weeks. Hence, all the patients included in this study took a total dose of 4 capsules (200mg) in four divided doses in two weeks and during this duration they also underwent hemodialysis regularly two times a week. The efficacy of sildenafil was assessed by repeating the IIEF questionnaire after two weeks of therapy. The drug was taken as efficacious (as per operational definition).

The safety of sildenafil was assessed by measuring the frequency of side effects of sildenafil administration (including headache, flushing, dyspepsia, palpitation and blurring of vision). Headache was measured on the basis of visual analogue score <5 was taken as a safe, while dyspepsia, flushing. palpitation and blurring of vision, on the basis of patient's symptoms are categorized as yes or no (as per operational definition).

Data analysis procedure

All the collected data was entered and analyzed through SPSS version 19. Numerical variables i-e age and IIEF score have been presented as mean ±SD. Categorical variables i-e efficacy and side effects have been presented as frequency and percentage. Data has been stratified for age, IIEF score and duration of renal failure to address effect modifiers. Post-stratification Chi-square test has been applied taking $p \leq 0.05$ as significant.

RESULTS

The age of the patients ranged from 40 years to 60 years with a mean of 48.55±5.61 years. Majority (n=86, 52.1%) of the patients were aged under 50 years. Duration of renal failure ranged from 6 months to 75 months with a mean of 42.86±19.41 months. Majority (n=69, 41.8%) of the patients had renal failure between 33-59 months followed by 57 (34.5%) patients who had renal failure between 6-32 months. The IIEF score at baseline ranged from 10 to 19 with a mean of 15.24±2.45. Majority (n=101, 61.2%) of the patients had baseline IIEF score in the range of 15-19. The follow-up IIEF score ranged from 17 to 25 with a mean of 22.25±1.84 and was significantly higher than that at the baseline. All these findings have been summarized in **Table 1.**

Erectile dysfunction improved in 145 (87.9%) patients. There was no significant difference in the frequency of efficacy across age (p=0.496), duration of renal failure (p=0.901) and baseline IIEF (p=0.543) groups as shown in **Table 2.**

Headache was the most frequent side effect and was reported by 27 (16.4%) patients followed by flushing (n=21, 12.7%), blurring of vision (n=9, 5.5%) and dyspepsia (n=7, 4.2%). Palpitation was not reported by any patient. These findings have been summarized in **Table 3**. There was no statistically significant difference in the frequency of any side effect across age, duration of renal failure and baseline IIEF score groups as shown in **Tables 4 to 7.**

Table (1): Baseline Characteristics of Study Population.

Characteristics	Participants (n=165)
Age (years), mean ±SD	48.55±5.61 (40 - 60)
Age Groups	
• <50 years	86 (52.1%)
• ≥50 years	79 (47.9%)
Dialysis Duration (months), mean ±SD Dialysis Duration Groups • 6-32 months • 33-59 months • 60-75 months	42.86±19.41 (6 - 75) 57 (34.5%) 69 (41.8%) 39 (23.6%)
Baseline IIEF Score, mean ±SD Baseline IIEF Score Groups • 10-14 • 15-19 Follow-up IIEF Score	15.24±2.45 (10-19) 64 (38.8%) 101 (61.2%) 22.25±1.84***

*** t-test comparing baseline and follow-up IIEF scores. Observed difference was statistically significant (p=0.000)

Table (2): Frequency of Efficacy (measured by variables percentages.

Characteristics	Efficacy [n (%)]	P-value
Overall	145/165 (87.9%)	-
Age Groups • <50 years • ≥50 years	 77/86 (89.5%) 68/79 (86.1%)	 0.496
Dialysis Duration • 6-32 months • 33-59 months • 60-75 months	 51/57 (89.5%) 60/69 (87.0%) 34/39 (87.2%)	 0.901
Baseline IIEF Score Groups • 10-14 • 15-19	 55/64 (85.9%) 90/101 (89.1%)	 0.543

Chi-square test. Observed difference was statistically insignificant.

Table (3): Frequency of Various Side Effects of Treatment.

Side Effects	n (%)
Headache	27 (16.4%)
Flushing	21 (12.7%)
Blurring of Vision	9 (5.5%)
Dyspepsia	7 (4.2%)
Palpitation	0 (.0%)

Chi-square test. Observed difference was statistically insignificant.

Table (4): Stratification of Headache.

Characteristics	Headache [n (%)[	P-value
Overall	27/165 (16.4%)	-
Age Groups <50 years ≥50 years	 13/86 (15.1%) 14/79 (17.7%)	 0.651
Dialysis Duration(months) 6-32 months 33-59 months 60-75 months	 6/57 (10.5%) 12/69 (17.4%) 9/39 (23.1%)	 0.252
Baseline IIEF Score Groups 10-14 15-19	 11/64 (17.2%) 16/101 (15.8%)	 0.820

Chi-square test. Observed difference was statistically insignificant.

Table (5): Stratification of Flushing.

Characteristics	Flushing [n (%)]	P-value
Overall	21/165 (12.7%)	-
Age Groups <50 years ≥50 years	 9/86 (10.5%) 12/79 (15.2%)	 0.363
Dialysis Duration Groups 6-32 months 33-59 months 60-75 months	 8/57 (14.0%) 8/69 (11.6%) 5/39 (12.8%)	 0.920
Baseline IIEF Score Groups 10-14 15-19	 7/64 (10.9%) 14/101 (13.9%)	 0.583

Chi-square test. Observed difference was statistically insignificant

Table (6): Stratification of Blurring of Vision.

Characteristics	Blurring of Vision [n (%)]	P-value
Overall	9/165 (5.5%)	-
Age Groups <50 years ≥50 years	 4/86 (4.7%) 5/79 (6.3%)	 0.635
Dialysis Duration Groups 6-32 months 33-59 months 60-75 months	 2/57 (3.5%) 4/69 (5.8%) 3/39 (7.7%)	 0.666
Baseline IIEF Score Groups 10-14 15-19	 4/64 (6.3%) 5/101 (5.0%)	 0.720

Chi-square test. Observed difference was statistically insignificant.

Table (7): Stratification of Dyspepsia.

Characteristics	Dyspepsia [n (%)]	P-value
Overall	7/165 (4.2%)	-
Age Groups <50 years ≥50 years	 4/86 (4.7%) 3/79 (3.8%)	 0.786
Dialysis Duration Groups 6-32 months 33-59 months 60-75 months	 2/57 (3.5%) 3/69 (4.3%) 2/39 (5.1%)	 0.926
Baseline IIEF Score Groups 10-14 15-19	 3/64 (4.7%) 4/101 (4.0%)	 0.821

Chi-square test. Observed difference was statistically insignificant.

DISCUSSION

Medical Erectile dysfunction is the inability to achieve or maintain an erection for a satisfactory sexual performance. Advanced chronic kidney disease (CKD) is associated with erectile dysfunction (ED) in males.[1] Sexual dysfunction in patients with chronic kidney disease comprises both physiological (Hormonal, vascular, neurological) and psychological factors.[3] Dialysis improves most symptoms of end stage renal disease (ESRD), yet many patients continue to experience erectile dysfunction (ED) during the dialysis treatment. Different drugs have been used to treat erectile dysfunction in patients with chronic kidney disease like Yohimbine, Delequamine, Trazodone, Red Korean Ginseng, Limaprost, Phentolamine in ancient times but all of these drugs have unknown mechanism of action and less safety and efficacy.[5]

There were few international studies on the use of Sildenafil citrate for erectile dysfunction in hemodialysis patients but no such local published material could be found. The objective of this study was to find the efficacy and frequency of side effects of sildenafil citrate in patients on chronic hemodialysis with erectile dysfunction (E.D). It was a descriptive case series conducted at Department of Urology, Services Hospital, Lahore over 6 months.

This study involved 165 patients of renal failure on hemodialysis for at least six months presenting with erectile dysfunction. A written informed consent was obtained from every patient. The mean age of the patients was 48.55±5.61 years. A similar mean age was observed by Arslan et al. (49.3±13.2 years) and Yeniçerioglu et al. (49.8±9.1 years) in Turkish and Seibel et al. (49±10 years) in Brazilian patients of renal failure on hemodialysis presenting with erectile dysfunction. [7,10,12] Tas et al. however observed relatively lower mean age of 41.2±2.6 year among Turkish patients.[13] Majority (n=86, 52.1%) of the patients were aged under 50 years. Messina et al. also observed similar proportion of under 50 age group (53.5%) in Brazil.[2] The mean duration of renal failure was 42.86±19.41 months in the present study. Seibel et al. (42±31 months) in Brazil, Tas et al. (41.2±2.6 months) in Turkey and Ghafari et al. (44.5±11.17 months) in Iran observed similar mean duration of renal failure among patients presenting with erectile dysfunction.[7,11,13] Messina et al. however reported quite lower mean duration of renal failure (30.4±28.4 months) in Brazilian patients.[2]

The mean IIEF score at baseline was 15.24±2.45. It improved significantly (p=0.000) to 22.25±1.84 upon follow-up. A similar significant improvement in IIEF score with sildenafil citrate among such patients was previously reported by Yeniçerioglu et al. (25.2±5.5 vs. 15.2±6.0; p<0.05), Seibel et al. (23.0±5.7 vs. 16.00±4.8; p<0.001) and Tas et al. (23.0±1.4 vs. 19.8±1.0).[7,14]

Erectile dysfunction improved in 145 (87.9%) patients. There was no significant difference in the frequency of efficacy across age (p=0.496), duration of renal failure (p=0.901) and baseline IIEF (p=0.543) groups. A similar efficacy of sildenafil citrate in erectile dysfunction has been reported previously by Seibel et al. who observed it to be 85%.[7] Sahin et al. (74.5%) and Tas et al. (50%) reported comparatively lower efficacy of sildenafil.[9,13]

Headache was the most frequent side effect and was reported by 27 (16.4%) patients followed by flushing (n=21, 12.7%), blurring of vision (n=9, 5.5%) and dyspepsia (n=7, 4.2%). There was no statistically significant difference in the frequency of any side effect across age, duration of renal failure and baseline IIEF score groups. Our results match with those of Coelho et al. who observed similar frequency of headache (16.5%), flushing (14.0%), blurring of vision (5.1%) and dyspepsia (4.8%) with sildenafil citrate.[15] Moreira et al. also observed similar frequency of blurring of vision (5.8%).[16] A similar frequency of headache was also observed by Yeniçerioglu et al. (18.0%) and Ghafari et al. (20.0%).[11] Moreira et al. (25.4%) and Padma-nathan et al. (39.0%) observed much higher frequency of headache with sildenafil treatment [14,16] while Lim et al.

reported much lower frequency of 1.97%.[17] Fink et al. (12.0%), Morales et al. (10.0%) and Ghafari et al. (16.0%) reported similar frequency of flushing.[18,19] While Moreira et al. (30.8%) and Padma-nathan et al. (34.0%) observed much higher frequency of flushing with sildenafil treatment.[14,16] Sahin et al. reported flushing in only 1.8% patients.[9] Fink et al. also observed similar frequency of 5% for dyspepsia.[18] A relatively higher frequency of dyspepsia was observed by Morales et al. (7.0%) and Ghafari et al. (10.0%).[11,16] Palpitation was not reported by any patient in the present study. Our observation is in line with that of Coelho et al., Fink et al., Moreira et al., Padma-nathan et al., and Morales et al. who also didn't observed palpitation in any patient in their series.[14-16,18,19] Ghafari et al. (8.0%) and Sahin et al. (3.64%) however reported palpitation in patients treated with sildenafil.[9,11]

The present study is first of its kind in local population and has found the efficacy of sildenafil citrate be 87.9% in patients of renal failure on hemodialysis presenting with erectile dysfunction. This efficacy was unaffected by patients' age, duration of renal failure and baseline IIEF score. Headache was the most frequent side effect and was reported by 27 (16.4%) patients followed by flushing (n=21, 12.7%), blurring of vision (n=9, 5.5%) and dyspepsia (n=7, 4.2%). While no patient reported palpitation. The results of the present study are in line with the previous international studies in this regard with minor differences which can be due to population differences. The results of the present study advocate the use of sildenafil citrate in hemodialysis patients presenting in future practice for the treatment of erectile dysfunction.

CONCLUSION

The efficacy of sildenafil citrate was found to be 87.9% in patients of renal failure on hemodialysis presenting with erectile dysfunction. This efficacy was unaffected by patient's age, duration of renal failure and baseline IIEF score. Headache was the most frequent side effect and was reported by 27 (16.4%) patients followed by flushing (n=21, 12.7%), blurring of vision (n=9, 5.5%) and dyspepsia (n=7, 4.2%). While no patient reported palpitation.

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