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Association between PDE5 Inhibitors and Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION): A Descriptive Study

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Abstract **Original Research Article**

Objectives*:** Treatment by phosphodiesterase-5 (PDE-5) inhibitors for different medical illnesses in males has been reported to be a risk factor for development of non-arteritic anterior ischemic optic neuropathy (NAION). The objective was to review the relationship between PDE-5 inhibitors and the occurrence of NAION. ***Methods: This retrospective review descriptive research enrolled 532 male patients that used PDE-5 inhibitors. These patients were treated for erectile dysfunction in Jordanian Royal Medical Services between November 2020 and October 2024 for two periods of follow-up (30 days and 1 year). group1: patients with the use of PDE5Is for 30 days, group2: patients were given PDEIs for 1 year. Patients were aged between (46 and 78 years). Following variables were included in this research: NAION cases, underlying risk factor systemic disease, history of major surgery, and risk factor medications. ***Results*:** Regarding the demographic and categorical data no significant differences were observed except for the increase of the risk of NAION in group2 after prolonged use of PDE5Is > 30 days (group1 percentage of affected cases was 5.9%, while in group2 was 9.726%) (P value = 0.0492). ***Conclusion*:** NAION occurrence could be increased when treatment by PDE5Is last for a period more than one month. So, in contrast of other literatures that suggest no association between PDE5Is and occurrence of NAION, our study encourages further research to investigate the effect of these drugs on the circulation of the optic nerve head to decrease NAION possible cases.

Keywords: PDE5Is, NAION, Tadalafil, Sildenafil.

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INTRODUCTION

In males > 50 years, optic nerve injury most commonly leads to an acute condition called non-arteritic anterior ischemic optic neuropathy (NAION). Usually, the optic nerve head supplied by the short posterior ciliary arteries (SPCAs), and the infarction of the laminar or retrolaminar portion of this head caused by the impairment in these arteries. NAION usually gives the symptoms of sudden, painless, loss of vision in one or both eyes. By examination we can find decreased visual acuity, a visual field defect, decreased color vision, a relative afferent pupillary defect, and optic disc swelling. Until now, there are limited management options for NAION [1].

On the other side, the phosphodiesterase type 5 (PDE5) inhibitors (Avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, vardenafil and udenafil) are a drug class mainly approved for the treatment of erectile dysfunction, the treatment of signs and symptoms of benign prostatic hyperplasia, and pulmonary arterial hypertension [2].

(PDE5) inhibitors mechanism of action is to accumulate cyclic guanosine monophosphate and to increase release of nitric oxide by inhibiting the degradation of phosphodiesterase in the penile corpus cavernosum smooth muscle cells and subsequent vasodilation. The PDE-5 enzyme subtype, is specific for the corpus cavernosum, while PDE-6 subtype, is mainly

found in retinal blood vessels where sildenafil and vardenafil have been shown to have selectivity for these receptors as well; so, the transient changes in color perception that are commonly recognized side effects of these medications [3].

(PDE5) inhibitors are one of several factors that increase the risk of developing NAION. Other risk factors are optic nerve anatomy abnormalities like optic nerve head drusen and small cup-to-disc ratio or absence of the cup, increased age and genetic predisposition, underlying systemic diseases like (hypertension, episodic hypotension, hypercholesterolemia, diabetes mellitus, prothrombotic states, obstructive sleep apnea and blood loss), prolonged surgical procedures, cataract surgery, and medications like (amiodarone, interferon-a, nasal decongestants, and several vasopressors or vasoconstricting drugs) [4].

However, impact of (PDE5) inhibitors in the circulation of the optic nerve head or in the short posterior ciliary arteries has a little evidence [5].

Herein, we focused on the role of (PDE5) inhibitors as a risk factor for the increase of NAION incidence or not via the mechanism of action of these drugs and the pathophysiology that mentioned above.

METHODOLOGY

Retrospectively 532 male patients with the use of PDE-5 inhibitors were enrolled in this study. These patients were treated for erectile dysfunction and symptoms of benign prostatic hypertrophy in Jordanian Royal Medical Services between November 2020 and October 2024 for two periods of taking PDE5Is (30 days and 1 year). group1 (n=203): patients with recent history of taking PDE5Is (30 days), group2 (n=329): patients who were given PDE5Is for 1 year ages of the patients were between (46 and 78 years).

Inclusion Criteria:

Ages between (46 and 78 years), patients with underlying systemic diseases like (hypertension, hypercholesterolemia, diabetes mellitus, prothrombotic states, obstructive sleep apnea and anemia), history of prolonged surgical procedures, history of cataract surgery, and drug history of medications like (amiodarone, nasal decongestants, and vasopressors or vasoconstricting drugs).

Exclusion Criteria: past history of NAION, ages < 46 and > 78 years, and intermittent use of PDE5Is (every one week or more).

Data were expressed as mean ± SD. Statistical analysis was done. A *t* test was used for continuous variables and a chi square test was used for categorical variables by using SPSS v26 program. P values < 0.05 were considered to be statistically significant.

Ethical approval was gained from our ethical approval institution in Jordanian Royal Medical Services.

RESULTS

Total number of patients was 532 male patients with history of PDE5Is use. Group1 (n=203) ages (46-72 years), and group2 (n=329) ages (47-78 years). Regarding the demographic data no significant differences were seen (Table 1). Significant P value < 0.05.

Table 1: The demographic data

Variables	Group1 (N©=203)	Group2 (N=329)	P value
Ages (mean ± SD* years)	59± 14.54	61± 16.72	0.081
Hypertension (N\%®)	127\63%	248\75%	0.073
Hypercholesterolemia (N\%)	97\48	142\43%	0.092
Diabetes mellitus (N\%)	86\42%	103\31%	0.069
Prothrombotic states (N\%)	5\2.5%	7\2%	0.075
Obstructive sleep apnea (N\%)	1\0.5%	1\0.3%	0.072
Anemia (N\%)	12\6%	25\7.6%	0.097
Prolonged surgical procedures (N\%)	8\4%	10\	0.082
History of cataract surgery (N\%)	21\10.3%	27\8.2%	0.077
Drug history of medications like (amiodarone, nasal decongestants, and vasopressors or vasoconstrictors) (N\%)	4\2%	8\2.4%	0.087

N©: Number of the patients. SD*: standard deviation. %®: percentage of patients in relation to the total number of patients for each group.

In categorical data there were increase of NAION cases in the group that used PDE5Is for 1 year period prior to the disease including the three types of PDE5Is (tadalafil, vardenafil, and sildenafil) (table2). Significant P value < 0.05.

Table 2: Categorical Data

Variables	Group1 (N©=203)	Group2 (N=329)	P value
Total cases of NAION (N\%®)	12\5.9%	32\9.726%	0.0492
Tadalafil cases of NAION (N\%®)	5\2.5%	12\3.7%	0.0471
Vardenafil cases of NAION (N\%®)	3\1.5%	11\3.34%	0.0452
Sildenafil cases of NAION (N\%®)	4\2%	9\2.7%	0.0438

N©: Number of the patients. %®: percentage of patients in relation to the total number of patients for each group.

DISCUSSION

We noticed in our research that no significant differences in demographic data, but there was an increase number of NAION cases between recent taking of PDE5Is (30 days) and prolonged treatment (1 year) in favor of prolonged treatment.

Most literatures suggested that no supported evidence that PDE5 inhibitors can cause non-arteritic anterior ischemic optic neuropathy (NAION) [6-11], in contrast of our results.

Other literatures reported that the relationship between PDE5Is use and NAION is exist in rare cases and therefore precautions should be taken while using these medications. So, patients in regular use of PDE5 inhibitors and having other risk factors like DM, should be warned about the possibility of ischemic ocular side effects and seeking attention if they have visual field or acuity loss after using these drugs, avoid these medications if there was history of NAION in one eye, and physicians should advice PDE5 inhibitors carefully after considering that their benefits outweigh the probable severe adverse events [12-14].

On the other hand, many researches supported our results in the increasing risk of NAION to twofold in regular users or after prolonged use of PDE5Is in comparison those who took PDE5Is in more prior time or for a short period [15-18].

CONCLUSION

The risk of NAION could be increased when treatment by PDE5Is last for a long period (1 year) or in regular users > 1 month. So, while some literatures suggest that no association between PDE5Is and occurrence of NAION, and others supported this relationship, we encourage further investigations to understand the mechanism of action of these drugs in the impairment of the circulation at the optic nerve head and to avoid the damage of this nerve and therefore the NAION cases.

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