SEXUAL MEDICINE REVIEW

The Association Between Phosphodiesterase Type 5 Inhibitor Use and Risk of Non-Arteritic Anterior Ischemic Optic Neuropathy: A Systematic Review and Meta-Analysis

Bing Liu, MD,[1,†] Linxin Zhu, MM,[1,†] Jingxiang Zhong, MD,[1] Guohua Zeng, MD,[2,3,4] and Tuo Deng, MD[2,3,4]

ABSTRACT

Introduction: Phosphodiesterase type 5 inhibitors (PDE5-Is) are first-line drugs for erectile dysfunction. Non-arteritic anterior ischemic optic neuropathy (NAION) has been linked with PDE5-I use. However, no meta-analysis or conclusive review has explored the association between NAION and PDE5-I use.

Aim: To investigate the association between PDE5-I use and risk of NAION.

Methods: A comprehensive literature search was conducted using online databases in October 2017 to obtain studies researching the association between PDE5-I application and occurrence of NAION. Summarized unadjusted risk ratios (RRs) with 95% CIs were calculated for the strength of this association. This study was conducted in accordance to Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and registered in PROSPERO under number CRD42017080865.

Main Outcome Measures: The strength of association between PDE5-I use and risk of NAION was assessed through pooled unadjusted RRs and 95% CIs.

Results: 5 original articles with 6 clinical observations were included in the meta-analysis. No significant higher risk of NAION was observed after the use of PDE5-Is within a 1-month period (RR = 1.16, 95% CI = 0.98-1.39, P = .09). Subgroup analyses indicated 2 PDE5-Is were significantly related to NAION (tadalafil: RR = 2.14, 95% CI = 1.20−3.84, P = .01; sildenafil: RR = 2.25, 95% CI = 1.29−3.94, P = .004).

Conclusions: Although we found no association between NAION and PDE5-I use, our results should be interpreted cautiously because we included only observational studies and could not control for potential confounders. Because NAION is a rare ocular disease and difficult to diagnose, this association should be confirmed in prospective comparative studies with larger samples and more rigorous designs. **Liu B, Zhu L, Zhong J, et al. The Association Between Phosphodiesterase Type 5 Inhibitor Use and Risk of Non-Arteritic Anterior Ischemic Optic Neuropathy: A Systematic Review and Meta-Analysis. Sex Med 2018;X:XXX−XXX.**

Key Words: Association; Meta-Analysis; Non-Arteritic Anterior Ischemic Optic Neuropathy; Phosphodiesterase Type 5 Inhibitors; Systematic Review

INTRODUCTION

Erectile dysfunction (ED) is a disorder affecting approximately 1% to 10% of men younger than 40 years old. The prevalence rate increases to 20% to 100% in men older than 60 years.[1] Older age plays a vital role in the existence of ED, although other lifestyle factors are related to the onset of ED, such as tobacco or alcohol abuse, lack of exercise, obesity, sleeping disorders, and so on.[2] The interaction of ED with different systematic diseases such as diabetes also has been researched.[3]

Phosphodiesterase type 5 inhibitors (PDE5-Is) are first-line drugs for ED and have proved effective and relatively safe. Common mild adverse events include transient headache, dizziness, and blurred vision; however, some rare ocular complications can occur, leading

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[1]Department of Ophthalmology, First Affiliated Hospital of Jinan University, Guangzhou, China;

[2]Department of Urology, Minimally Invasive Surgery Center, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China;

[3]Guangzhou Institute of Urology, Guangzhou, China;

[4]Guangdong Key Laboratory of Urology, Guangzhou, China

[†]Equivalent contribution.

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to serious harm to patients' visual acuity.[4] Non-arteritic anterior ischemic optic neuropathy (NAION) has been linked to PDE5-I use. These patients often complain of unilateral, sudden, and painless loss of vision when awakening. Although the detailed pathogenesis is unclear, NAION is considered to be caused by hypoperfusion of ciliary arteries owing to systematic hypotension or some vascular diseases, without evidence of arteritis.[5] PDE5-Is block PDE5 to degrade cyclic guanosine monophosphates, which maintain relaxation of vascular smooth muscle. Cyclic guanosine monophosphates are activated and upregulated by the release of nitric oxide, so PDE5-Is could amplify the pharmacologic effect of nitric oxide donors.[6] PDE5 mainly exists in the corpus cavernosum, but some PDE5-Is such as sildenafil and vardenafil also act on the PDE6 subtype appearing in ocular blood vessels.[7] Although hypoperfusion caused by PDE5-Is might play a role in NAION, ED and NAION supposedly share some risk factors such as smoking, diabetes, and obstructive sleep apnea.[8]

Since 2005, after extensive reports about NAION and its potential association with PDE5-I use, the Food and Drug Administration (FDA) mandated pharmaceutical companies place warnings on their drug inserts and perform prospective studies to determine whether there is an association between PDE5-I use and NAION. In a case-crossover study sponsored by Pfizer and performed by Campbell et al,[9] a doubly increased risk of NAION was found in patients who recently used a PDE5-I compared with those who used a PDE5-I in a more remote period. A similar study sponsored by Eli Lilly was completed in February 2016 but has not been published (NCT01131104)[10] and a study sponsored by Bayer is ongoing (NCT00867815).[11] In an analysis by Pomeranz[12] of data on adverse events from the FDA, reports of ischemic optic neuropathy associated with PDE5-I use were more numerous than the number of cases from the published literature. However, some previous articles also reported no significant association between NAION and PDE5-I use[13,14] and the causality between them could not be elucidated clearly in current publications. Therefore, we conducted a systematic review and meta-analysis to investigate their association through combined statistics to provide some further evidence for the occurrence of NAION and rational use of PDE5-Is.

METHODS

This systematic review and meta-analysis was conducted in accordance to Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. The protocol of this review was registered in PROSPERO (registration number CRD42017080865).

Search Strategy

A comprehensive literature search was conducted using the PubMed, Embase, Cochrane Library, CBM, CNKI, and VIP databases and the last search was in October 2017. No data range criteria were applied when searching the original studies. Unpublished data were screened in databases such as OpenGrey and Web of Science. Search terms were *phosphodiesterase type 5 inhibitors* or *PDE5-Is* or *PDE5A inhibitors* or *PDE5 inhibitors* or *PDEIs* and *non-arteritic anterior ischemic optic neuropathy* or *NAION*. No language restriction was applied and references of related studies were scanned.

Inclusion and Exclusion Criteria

We defined study eligibility according to PICOS (patient population, intervention or exposure, comparator, outcome, and study design; Supplementary Figure 1). Studies focusing on the association between PDE5-I use and risk of NAION were included. Unadjusted relative ratios (RRs) or odds ratios (ORs) in these studies were extracted directly or were calculated. Editorials, reviews, conference proceedings and abstracts, case reports, animal experiments, and repeated publications were excluded. 2 reviewers (B.L. and L.Z.) independently screened related records meeting the inclusion criteria, and disagreement was resolved by a 3rd reviewer (T.D.).

Data Extraction and Quality Assessment

Data from included studies were checked carefully and extracted by 2 independent reviewers. The following information was collected on a prepared standard form: first author, year of publication, country, ethnicity, study period, type and timing of PDE5-I use, case and control sample sizes, and number of patients with NAION. RRs or ORs for the risk of NAION from PDE5-I use also were extracted, if possible.

The level of evidence of each study was accessed by the GRADE approach by 2 reviewers independently.[15] The quality of non-randomized controlled trials also was assessed by the Newcastle-Ottawa Scale.[16] Literature with an assessment score of at least 7 stars was considered high quality.

Statistics Analysis

Unadjusted RRs or ORs of PDE5-I use for the risk of NAION were extracted or calculated from all studies with their 95% CIs. Pooled unadjusted RRs and 95% CIs were calculated to assess the strength of association between PDE5-I use and NAION. Subgroup analyses were conducted based on study region, study design, and type of PDE5-I. Apparent heterogeneity existed if the P value was less than 0.10 by χ^2 test[17] and the random-effect model was applied to achieve the pooled RR. Lack of heterogeneity was considered when the P value was higher than .10 and the fixed-effect model was used. Results in this study were regarded as significant only with a 2-sided P value less than .05. Publication bias was evaluated by inverted funnel plot visual inspection.[18] All statistical analyses were conducted by RevMan 5.3 (Cochrane Collaboration, Oxford, UK).

RESULTS

Characteristics and Quality Assessment of Included Studies

6 clinical trials from 5 studies were included in this study. More than 5 million patients were observed and researched for