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RESEARCH ARTICLE

CARDIOVASCULAR COMPLICATIONS OF OPHTHALMIC TIMOLOL AS SEEN IN PATIENTS IN SOUTH-SOUTH NIGERIA: CASE SERIES AND LITERATURE REVIEW

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ABSTRACT

Background: Timolol, a non-selective beta-blocker, is used in the treatment of Glaucoma. Despite its topical application, reports indicate the occurrence of cardiovascular side effects resulting from systemic absorption. Here, we present three case series illustrating the bradycardic impact of ophthalmic timolol.

Case Presentations: We report 3 cases of outpatients of Goodheart Medical Consultants Hospital who presented with symptoms such as dizziness and low pulse rate. Electrocardiography indicated a low heart rate of 48,52 and 53 beats per minute respectively. Although bradycardia resolved for the first 2 cases after discontinuing timolol it didn't resolve for the 3rd case.

Conclusion: Using ophthalmic timolol can trigger bradycardia, with discontinuation not always resolving the condition. Patients prescribed ophthalmic timolol should undergo regular cardiovascular monitoring. Immediate discontinuation of timolol is advised if any adverse effects are observed to prevent potential long-term consequences.

KEYWORDS: Timolol, Bradycardia, Case Report, Cardiovascular Complication, Ophthalmic, Glaucoma.

INTRODUCTION

Cardiovascular complications are a significant concern in glaucoma patients using ophthalmic timolol (1). Timolol, a nonselective beta-blocker, has served as the fundamental element in glaucoma treatment since its initial approval in the USA in 1978 (1) due to its effectiveness in reducing intraocular pressure (IOP) (2), having minimal occurrence of ocular side effects (3), and the absence of an impact on pupil size (4). Glaucoma is a progressive optic nerve condition that results in damage to the optic disc, causes visual impairment, and stands as the world's second most prevalent cause of blindness (5). The prevalence of glaucoma increases with age (6). A survey reveals that between 1.1 to 1.4 million adults in Nigeria are affected by glaucoma, with the majority unaware of their condition (7). The primary approach to managing glaucoma typically involves using prescription eye drops. These drops function by reducing the pressure within the eye, thereby safeguarding the33 optic nerve from harm. While these eye drops cannot cure glaucoma or restore lost vision, they impede the progression of the condition, preventing it from exacerbating (8). Beta-adrenergic antagonists, also known as beta-blockers (β-blockers), are the most frequently prescribed medications for glaucoma in several countries, including the United Kingdom (9) the United States (10), and in Nigeria (11). More than 40% of individuals with glaucoma or hypertension are prescribed beta-blockers, and almost half of newly diagnosed patients are initially treated with a beta-blocker, usually timolol (3).

Research suggests that a concentration of 0.5% ophthalmic timolol is equivalent to a 10mg oral dose (12) and when administered 80% of the medications are absorbed into systemic circulation(13). Timolol can enter the systemic circulation via the nasolacrimal duct, conjunctival vessels, and gastrointestinal tract (14–16) as a result, it bypasses the initial hepatic metabolism, resulting in heightened systemic exposure and impacting cardiac, pulmonary, central nervous system, and endocrine functions (14,17).

Though there are a handful of studies on the cardiac effects of ophthalmic timolol in developed countries, research is scarce on this issue in developing countries such as Nigeria. Hence, we report three (3) cases of patients in a cardiac center in Port Harcourt with glaucoma using ophthalmic timolol medication and aim to understand the potential effects of this medication on the cardiovascular system in individuals within this specific population.

METHODOLOGY

This study is a retrospective case series design to investigate the cardiovascular complications associated with the use of ophthalmic timolol in patients from the South-South region of Nigeria. A case series approach was used for the systematic collection and analysis of data from a small group of patients with similar characteristics or exposures. Cases was selected from patients who have visited ophthalmology clinics within this region.

Inclusion Criteria

- Patients diagnosed with glaucoma or ocular hypertension.
- Patients who have been prescribed ophthalmic timolol as part of their treatment regimen.
- Patients who have developed cardiovascular complications subsequent to the use of ophthalmic timolol.

Exclusion Criteria:

- Patients with incomplete medical records or insufficient documentation.

Medical records of eligible patients will be reviewed to collect relevant data including: Demographic information (age, gender, etc.), Diagnosis of glaucoma or ocular hypertension, Cardiovascular complications observed (e.g., bradycardia, hypotension, heart block, etc.).

Data was anonymized to ensure patient confidentiality.

Descriptive statistics was used to summarize the demographic and clinical characteristics of the case series.

CASE SERIES

Case Study 1

A 62-year-old hypertensive male, presented to our facility with complaints of dizziness, fatigue and faint feeling for the past few weeks. He reported no chest pain, shortness of breath, or palpitations. His primary concern was the persistent feeling of light-headedness, especially upon standing up from a seated or lying position. The patient indicated that he has been on ophthalmic timolol for the past year and that symptoms began a few months after being on the medication.

Vital signs were as follows; Temperature: 36.8^{o}C, Heart Rate: 48 beats per minute, Blood Pressure: 154/90 mmHg, Respiration: 20c/m, SPO2: 97%

Electrocardiogram (ECG) findings revealed; Early repolarization pattern, Sinus bradycardia (HR 48 bpm), Ischemic changes and T-wave abnormalities (fig 1). Comparison with a previous ECG showed a heart rate of 76 bpm before timolol use (fig 2).

Laboratory Investigations which included Full Blood Count (FBC), Troponin, Fasting Blood Glucose (FBG), Fasting Lipid Profile (FLP), Electrolyte/Urea/Creatinine (E/U/Cr) and Urinalysis (UA) were all within normal limits.

Considering the patient's symptoms and ECG findings, a diagnosis of bradycardia and possible cardiac ischemia was suspected. Given the patient's normal troponin levels and absence of other significant abnormalities in blood work and urinalysis, the possibility of acute coronary syndrome was less likely.

The patient was started on a combination of perindopril and amlodipine to control his blood pressure. Perindopril, an angiotensin-converting enzyme (ACE) inhibitor, would help in vasodilation and reducing blood pressure, while amlodipine, a calcium channel blocker, would further aid in blood pressure control without exacerbating bradycardia.

The patient was scheduled for regular follow-up visits to monitor his blood pressure and cardiac symptoms. He was advised to report any worsening of symptoms or the development of new symptoms promptly. Additionally,

an ophthalmology consultation was arranged to discuss alternative treatment options for glaucoma to avoid potential cardiovascular side effects associated with ophthalmic timolol.

Case Study 2

A 55-year-old hypertensive male, presented to the facility complaining of general body weakness, palpitations, and a low pulse rate. He first noticed the low pulse rate at home using his personal monitoring device. His symptoms had been ongoing for the past week, gradually worsening in intensity.

Vital signs showed: Blood Pressure: 140/80 mmHg, Temperature: 37°C, Heart Rate: 52 beats per minute Respiration Rate: 20 breaths per minute and SPO2: 98%

Investigations showed Serum Electrolytes/Urea/Creatinine (SEUCR), UA, Serum Phosphate (PO4) and Full Blood Count with Differential (FBC+DD) were all within normal limits.

However, ECG Findings showed Sinus arrhythmia, Poor R-wave progression, and T-wave abnormalities. 24-Hour Holter ECG Monitoring showed significant supraventricular ectopic while in the 24-Hour Ambulatory Blood Pressure Monitoring (ABPM), suboptimal blood pressure with a non-dipping pattern was observed.

Given the patient's clinical presentation and diagnostic findings, a multidisciplinary approach involving cardiology, internal medicine, and ophthalmology was initiated. The patient was started on the following medications:

- Clopidogrel: To prevent platelet aggregation and reduce the risk of thrombotic events.

- Rivaroxaban: As an anticoagulant to prevent the formation of blood clots.

- Amiodarone: To help control cardiac arrhythmias.

- Spironolactone: To manage any underlying cardiac issues and potentially reduce blood pressure.

- Telmisartan and Amlodipine Combination: To further control blood pressure and address any hypertension that may have been unmasked by the ophthalmic timolol.

The patient was referred to an ophthalmologist for a thorough evaluation of his ocular health and consideration of alternative medications for glaucoma. It was decided to discontinue ophthalmic timolol due to its potential adverse effects on the cardiovascular system, which were evident in this case.

Regular follow-up appointments were scheduled to monitor the patient's response to treatment, assess his cardiac rhythm, and optimize his blood pressure control. The patient was advised to report any new symptoms or concerns promptly.

The patient returned to the hospital a few days after discontinuing timolol and it was observed that his heart rate was normal (76b/m)

Case Study 3

A 52-year-old male diagnosed with hypertension and glaucoma, and currently using timolol, visited our facility for a routine examination. Although he did not mention any particular symptoms, he voiced worries regarding the management of his blood pressure and his general well-being. His vital signs were as follows: Blood Pressure: 140/90 mmHg, Temperature: 36.3°C, Heart Rate: 66 beats per minute, Respiration Rate: 20 breaths per minute, SPO2: 98%

Medical investigations reveled that his FBG, FLP and Urinalysis were within normal limits, but Serum Potassium was low, Serum Creatinine was Increased and D-dimer was elevated. ECG Findings showed Bradycardia (53 beats per minute) and Inverted T-wave (fig 3).

24-Hour Holter ECG Monitoring showed Occasional supraventricular ectopic with early morning bradycardia while ABPM showed Suboptimal blood pressure with a good dipping pattern.

Given the patient’s medical history and the findings from investigations, a comprehensive treatment plan was developed to address his cardiovascular and ocular health:

Dabigatran To prevent thromboembolic events and manage any underlying coagulation abnormalities indicated by the elevated D-dimer levels.

Perindopril/Amlodipine to control blood pressure through dual mechanisms of ACE inhibition and calcium channel blockade.

Spironolactone to manage hypertension and address the low potassium levels.

Atorvastatin to control lipid levels and reduce cardiovascular risk.

Potassium Supplement to replenish potassium levels and address hypokalaemia.

Due to concerns regarding the ocular side effects of the current medication regimen, the patient was referred to an ophthalmologist for further evaluation and management.

After review with the ophthalmologist, the patient was initially placed on travoprost, which unfortunately caused blurred vision. Subsequently, he was switched to bimatoprost, which also resulted in ocular side effects and a reduction in heart rate (fig 4). Given these complications, the ophthalmologist recommended either a lower dose of timolol or a combination therapy that would limit systemic absorption of the medication. The patient was then advised to return to the facility for further investigation and coordination of care.

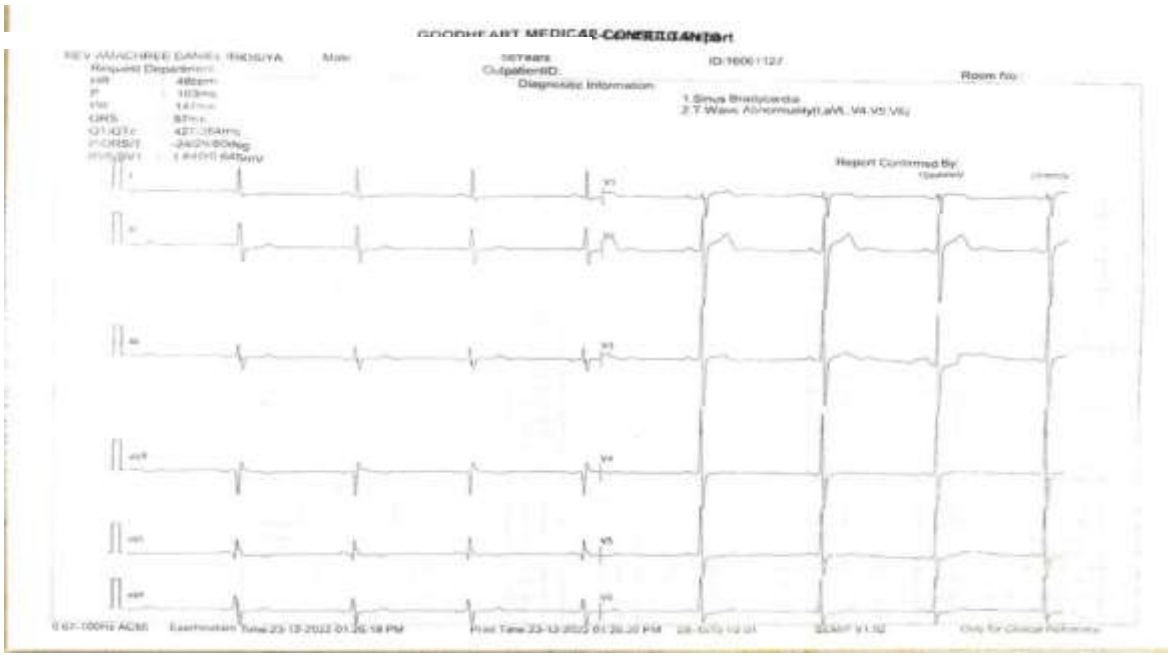

FIGURE 1- ECG of A Patient Showing Sinus Bradycardia and Ischemic Changes

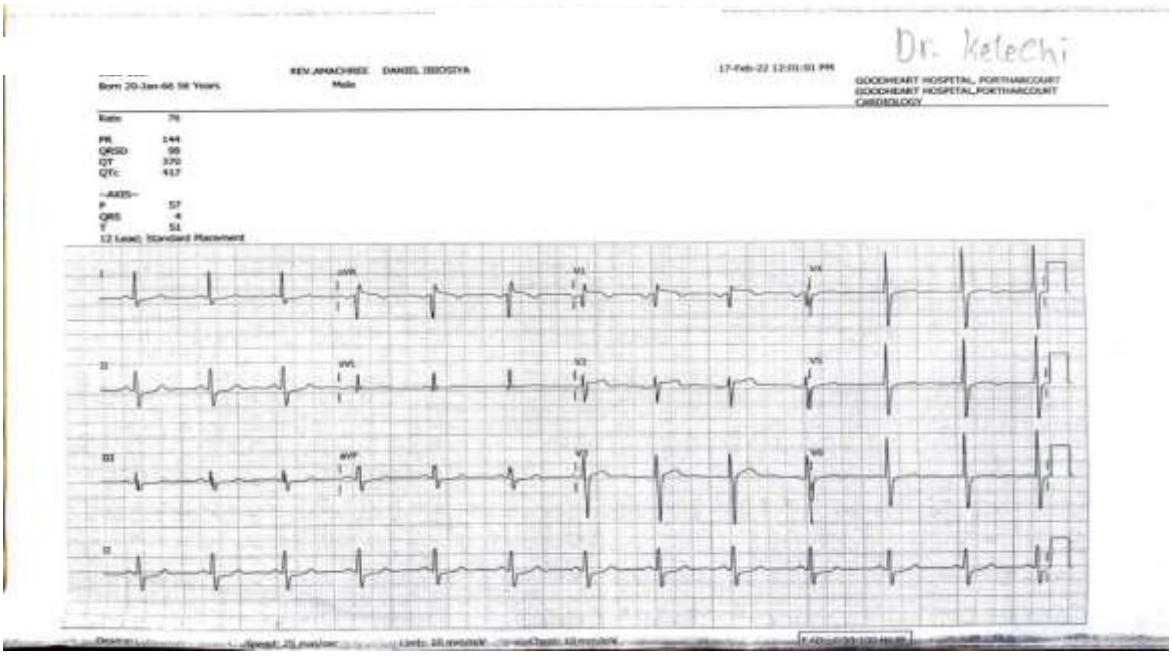

FIGURE 2- ECG of A Patient Showing Poor R-Wave Progression

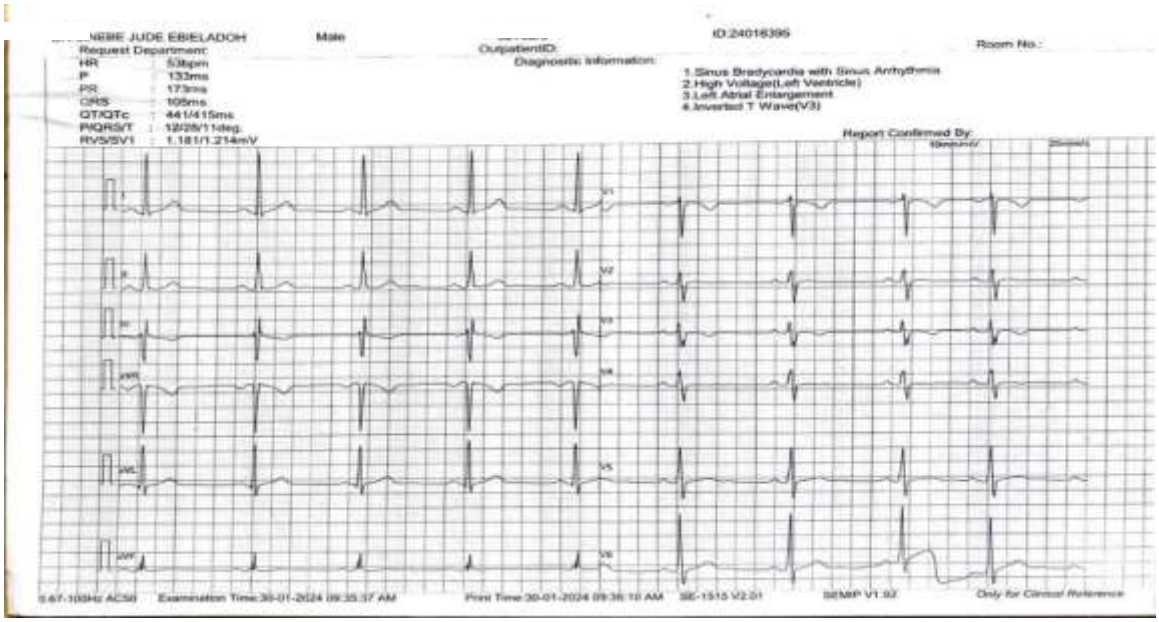

FIGURE 3- ECG of A Patient Before Ophthalmic Timolol Showing HR Of 53b/m

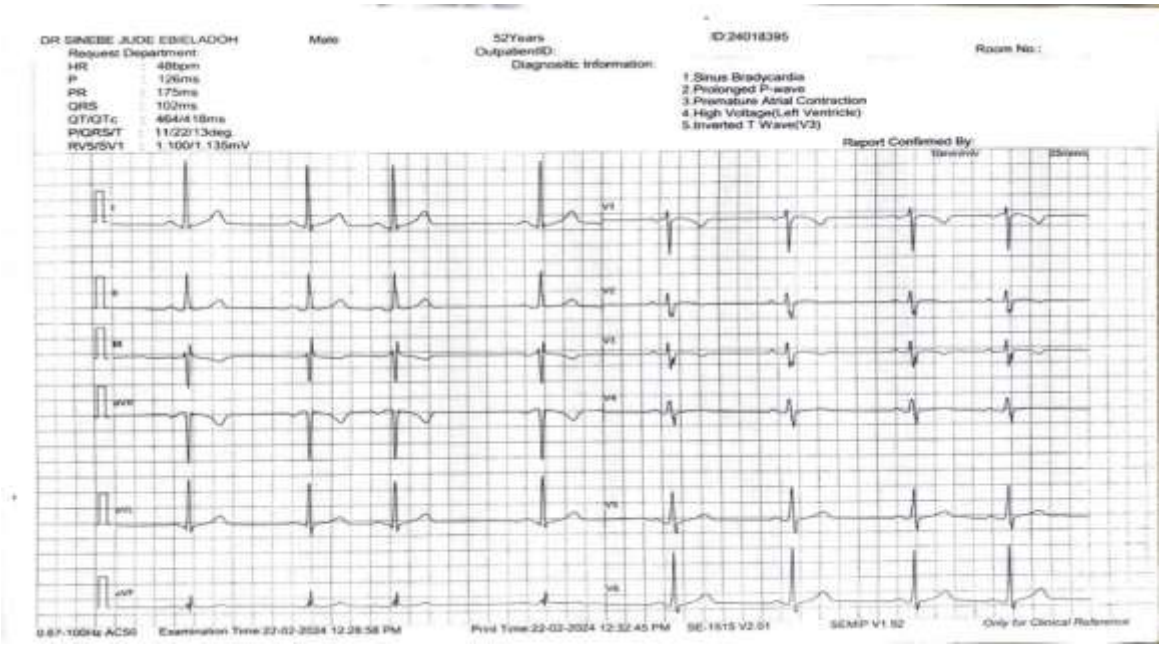

FIGURE 4- ECG of A Patient After Ophthalmic Timolol Showing HR Of 48b/m

TABLE 1- Individual Case Report Concerning Cardiovascular Adverse Effect in Patients Using Ophthalmic Timolol

Case study	Variables	Age	Medical History	Presenting Complaint	Heart rate before Timolol use	Heart rate during	Heart rate after
Case Study 1	Bradycardia	62	Hypertension	Dizziness, Fatigue, Faint feeling	NA	48	62
Case Study 2	Bradycardia	55	Hypertension	General body weakness, palpitation and low pulse rate	96	52	82
Case Study 3	Bradycardia	52	Hypertension	Fluctuating blood pressure and low pulse rate	63	53	48

DISCUSSION

From the three case studies, bradycardia was reported as the side effect of ophthalmic timolol (Table 1). This agrees with several studies where serious symptomatic bradycardia was observed in patients on ophthalmic timolol (12,18,19). This occurrence is due to the systemic absorption of the medication. Timolol, a beta-adrenergic blocker, can enter the bloodstream through the eye and inhibit beta-adrenergic receptors in the heart, leading to a decrease in heart rate. Despite evidence linking the use of topical β-blockers to bradycardia, dispensing of ophthalmic β-blockers with medicines which can cause or exacerbate bradycardia is common (12). It is necessary to implement interventions aimed at increasing awareness among prescribers about this potential adverse event. Given that ophthalmologists typically initiate most glaucoma treatments, while general practitioners may handle adverse events, there are challenges in addressing such events across the care continuum. Therefore, cross-specialty collaboration is essential to enhance patient care. This involves improving communication among ophthalmologists, general practitioners, pharmacists, and patients regarding cardiac history and glaucoma treatment, ultimately optimizing patient outcomes.

The presenting symptoms of patients from the first two case studies were dizziness, fatigue, shortness of breath and palpitations. Beta-blockers like timolol can affect the autonomic nervous system, leading to a decrease in heart rate and blood pressure (20) this can result in dizziness, especially upon standing up quickly, due to reduced blood flow to the brain as seen in the second case study.

As observed in the first and second case study, discontinuing timolol typically leads to a swift return to a normal sinus rhythm, often noticeable within several hours, particularly in cases where bradycardia was mild or moderate (18,21). Moreover, in instances of accelerated idioventricular rhythm (AIVR), the arrhythmia resolved within a few hours(22).

From our third case study, we could see that even after the patient had discontinued timolol he still had bradycardic episodes. This is similar to a case study where the patient who after discontinuing timolol still had several episodes of bradycardia for days (23). Explaining the bradycardic course observed in this patient poses a challenge; however, two possible explanations may be considered. Firstly, there could be a potential remodelling of the autonomic nervous system. Anticipating the remission of bradycardia within a few hours after discontinuing timolol, especially when the medication has been administered over several years, presents certain complexities (23). Secondly, there is a possibility of timolol accumulation in the liver or eye (24) nevertheless, such a mechanism lacks substantial documentation, and prevailing opinion suggests no evidence of significant drug accumulation.

CONCLUSION

This case studies highlights the importance of considering medication-induced side effects, even in patients without known comorbidities. Ophthalmic timolol, although effective in managing glaucoma, can lead to significant systemic absorption and subsequent cardiovascular complications. Close collaboration between specialties, including cardiology, internal medicine, and ophthalmology, is important in managing such cases effectively while prioritizing patient safety and well-being. Regular monitoring and adjustment of medication regimens based on individual patient responses are essential for optimizing outcomes.

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