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# Safety Concerns of Glaucoma Chemotherapy among G6PD Deficient Glaucoma Patients: A Pilot Study

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## Abstract

**Purpose:** The aim of this study was to assess the potential acute adverse effects associated with the use of anti-glaucoma medications among glaucoma patients with Glucose-6-Phosphate Dehydrogenase deficiency.

**Materials and Methods:** A prospective case-control study was piloted in the ocular and haematological assessment of newly diagnosed glaucoma patients. G6PD enzymopathy screening, haematological and ocular assessments were done prior to the dispensary of anti-glaucoma medications. Ocular assessments included Slit lamp bio microscopy of conjunctiva coloration and crystalline lens transparency and funduscopic evaluation of the retinal background for hemorrhages, exudates, degenerations and vascular changes. Haematological assessment included assessment of the red blood cell counts, hematocrit, and haemoglobin and serum bilirubin levels. These ocular and haematological assessments were repeated in two consecutive reviews at monthly intervals a month after the start of the initial therapy to identify any ocular and haematological changes among cases and controls.

**Results:** There were 116 glaucoma patients with mean age of 61.28 ± 16.62 years. A G6PD enzymopathy prevalence of 15.56% was recorded with 16 participants being cases (full G6PD defect) and 98 as controls (no G6PD defect). Also, 72.22% were males with the remaining 27.78% being females ($\chi^2 = 7.484$, $p = 0.024$). Mixed repeated measures ANOVA analysis did not indicate significant acute changes in the ocular parameters and haematological profiles in the pretreatment and follow up findings among the cases and controls for each anti-glaucoma medication assessed and all the anti-glaucoma medications in general.

**Conclusion:** There was no acute ocular and haematological adverse effects associated with the use of anti-glaucoma medications among G6PD deficient glaucoma patients.

**Keywords:** Glaucoma; Glucose-6-Phosphate Dehydrogenase; Hemolytic Anemia; Ocular Adverse Effect; Carbonic Anhydrase Inhibitors

## Introduction

Although a number of red blood cell (RBC) enzyme deficiencies have been identified, Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency continues to take the lead as the most common human enzyme defect and as one of the most common genetic disorders worldwide [1]. It is estimated that a total of 400 million people worldwide carries the mutation in the G6PD gene that causes deficiency of this enzyme [2]. G6PD is an important enzyme in the glucose oxidation process of red blood cells (RBCs) and the maintenance of their normal life span. This enzyme triggers the production of reducing powers to all cells in the form of NADPH (Nicotinamide Adenine Dinucleotide Phosphate) by catalyzing the first reaction in the Pentose Phosphate Pathway (PPP). NADPH enables cells to counterbalance oxidative stress that can be triggered by several oxidant agents and to preserve the reduced form of glutathione (GSH). The PPP is the only source of NADPH for the red blood cells since they lack mitochondria and therefore their defense against oxidative damage is dependent on G6PD enzyme activity.

Mutations in the G6PD gene, located on the X chromosome, are responsible for causing the disease by reducing the amount of G6PD enzyme in the blood or altering its structure. A male with the mutation on the X chromosome will have low enzyme activity

as compared to females with mutation on both XX chromosomes (full defect). A female who has a mutant G6PD gene on one of her X chromosome is a carrier for G6PD deficiency thus has moderate G6PD enzyme activity (partial defect).

A variety of drugs and infections have been named to cause hemolytic anemia and non-hematologic sequelae in persons with the deficiency. The Sulphonamides and its derivative, the Carbonic anhydrase inhibitors (both topical drops and systemic pills dosage forms): Dorzolamide, Brinzolamide and Acetazolamide, are popular anti-glaucoma agents which have been labeled as potentially contraindicated in patients with G6PD deficiency [3]. This assertion however lacks adequate clinical evidence as the drugs contraindicated are used routinely in ophthalmic practice. Other studies which attempted to verify the potential effect of glaucoma medication in G6PD deficiency adopted an *in-vitro* approach which has inherent challenges in informing clinical decision [4].

Patients suffering from glaucoma are usually placed on anti-glaucoma medications on a lifetime basis heightening the risk of potential ocular and systemic adverse effects. Therefore, a better understanding of the safety profile of ophthalmic medications used as anti-glaucoma agents in G6PD deficiency is important due to the implications for treatment-oriented decisions, particularly in the long term management of this disease. The objective of this study was to review the acute adverse effects associated with the use of anti-glaucoma medications in the management of glaucomas among patients with Glucose-6-Phosphate Dehydrogenase deficiency. This is intended to inform ophthalmic practitioners on the need to establish the G6PD deficiency status of their glaucoma patients before prescribing anti-glaucoma agents for them or otherwise. It was also to inform prescribers on the peculiar acute adverse effects associated with the use of these drugs among G6PD deficient glaucoma patients.

## Materials and Methods

This was a prospective case-control pilot design involving 116 newly diagnosed glaucoma patients recruited at the Bishop Ackon Memorial Christian Eye Center. Glaucoma diagnosis was by the attending glaucoma specialist and it was based on optic nerve head integrity, retinal nerve fiber layer analysis, visual field testing, pachymetry and intra-ocular pressure findings.

A purposive sampling method was used to recruit 116 newly diagnosed glaucoma patients into the study. These patients were placed on anti-glaucoma medications by their caregivers which included Timolol (a non-selective beta blocker administered topically twice daily), Travaprost (a prostaglandin analogue administered topically ones daily), Brimonidine (an adrenergic alpha-agonist administered topically twice daily), Brinzolamide (Topical carbonic anhydrase inhibitor administered topically twice daily) and Acetazolamide (Oral carbonic anhydrase inhibitor administered orally 250mg twice daily for a week).

These patients were then tested for their G6PD deficiency status with those being G6PD deficient considered as cases and those without the defect as controls. In this study, clinical ocular assessment of participants was performed prior to them being dispensed with anti-glaucoma medications by their caregivers. These included Slit lamp bio microscopy (ZEISS SL 220, Germany) to evaluate the conjunctiva coloration (pigmentation, redness and yellowness) and the crystalline lens transparency. Direct fundoscopy using Welch Allyn Direct Ophthalmoscope under dim illumination was performed to assess the integrity of the retinal background for the presence of chorioretinal degenerations, vascular tortuosity, exudates and hemorrhages. Additionally, Slit lamp mounted applanation tonometry and manual blood pressure measurements were performed. Their blood samples were then taken to investigate their G6PD enzyme deficiency status using Methaemoglobin reduction test. Full blood count (haemoglobin, hematocrit, red blood cells) and serum bilirubin levels were as well assessed using a hematology analyzer (Midray BC-2800 hematology analyzer, China) and chemical analyzer (Advanced Instruments Model BR2 Bilirubin Stat-Analyzer, USA) respectively. The hematology analyzer used Electrical impedance principle to estimate the full blood count parameters. Glaucoma patients who were already on anti-glaucoma medications and those receiving treatment for other co-existing ocular pathologies and systemic conditions were excluded from the study. Also, glaucoma patients aged below 18 years were excluded from the study.

Subjects were reviewed monthly, on two consecutive visits during which all the eye examinations conducted during the pre-clinical assessment were repeated. Full blood count profile and serum bilirubin levels of the subjects were reassessed during each monthly review.

## Data Analysis

Data obtained was analyzed with the statistical package for social sciences to establish a comparison between the pretreatment findings and the review findings of the G6PD deficient participants (cases) and non-G6PD deficient participants (controls) using mixed repeated measures ANOVA. Descriptive results were expressed as frequency, percentage, and mean ± standard deviation. Chi-square statistical analysis was used to test for associations between categorical and non-numerical variables.

## Ethical Considerations

The study was conducted in accordance with the Helsinki Declaration on Research Regarding Human Subjects. Ethical clearance was obtained from the Institutional Review Board of the University of Cape Coast (Ethical clearance ID: UCCIRB/CHAS/2017/53). All protocols followed were strictly in line with the ethical standards of the Ghana Health Service. Consent was sought from all

participants and they were made to understand they could withdraw from the study at any time. Anonymity and confidentiality was ensured by blinding the identity of participants with unique identifiers. Each participant was informed and educated on their G6PD status during the first review visit. G6PD status screening cards were as well given to participants to be kept as part of their medical documents. Participants with the full G6PD defects were extensively educated on the implications of their G6PD status and encouraged to present their G6PD screening status cards to their clinicians when seeking medical or pharmaceutical care. The ocular and haematological changes in each participant were monitored to prompt their attending clinicians should there be any threatening changes and complications for appropriate actions to be taken. However, none of such cases was recorded during the study to necessitate such prompting.

## Results

Out of the 830 glaucoma patients who reported to the study facility during the study period, a total of 116 met the inclusion criteria and were recruited into the study. The participants had an average age of 61.28 ±16.62years. A total of 96 subjects (82%) were diagnosed of Primary open angle glaucoma, 10 (8.6%) Normal tension glaucoma, 8 (6.9%) Juvenile glaucoma, 2 (1.7%) Secondary glaucoma. A G6PD prevalence of 15.56% was established with a gender association ($\chi^2 = 7.484$, $p = 0.024$) as summarized in Table 1 below.

| G6PD Screening | Male | Female |
|---|---|---|
| No defect | 50 (43.10%) | 48(41.38%) |
| Partial defect | 0 (0.0%) | 2 (1.72%) |
| Full defect | 13 (11.2%) | 3 (2.6%) |
| **Total** | **63 (54.3%)** | **53 (45.7%)** |

**Table 1:** Gender and G6PD Status

Out of the 166 subjects who were recruited into the study, a total of 61 (52.59%) subjects participated in the two scheduled review assessments after the pretreatment assessment. Of these, 13 subjects had the G6PD enzymopathy (cases) with the remaining 48 (78.69%) subjects having no defect (controls). Data from these subjects were therefore analyzed and compared. Anti-glaucoma agents assessed included; Timolol maleate only, Travoprost only, Timolol maleate Brimonidine combination, Timolol maleate Brinzolamide combination and Travoprost Acetazolamide combination.

## Ocular Assessments

No significant acute changes were indicated in the ocular structures of both eyes among the various G6PD statuses for all the antiglaucoma medications used (Table 2).

| | P-Value | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Timool | | | Travaprost | | | Timolol & Brimonidine | | | Timolol & Brinzolamide | | | Travoprost & Acetazolamide. | | |
| | PT | R1 | R2 | PT | R1 | R2 | PT | R1 | R2 | PT | R1 | R2 | PT | R1 | R2 |
| **Redness** | 0.677 | 0.784 | 0.198 | 0.665 | 0.899 | 0.899 | 0.650 | 0.650 | 0.813 | 0.500 | 1.000 | 1.000 | 1.0 | 1.000 | 1.000 |
| **Pigmentation** | 0.660 | 0.859 | 0.819 | 0.756 | 0.513 | 0.582 | 0.660 | 0.607 | 0.285 | 1.000 | 1.000 | 1.000 | 0.400 | 1.000 | 0.400 |
| **Yellowing** | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.0000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| **Lens opacities** | 0.518 | 0.372 | 0.833 | 0.552 | 0.565 | 0.432 | 0.540 | 0.608 | 0.644 | 0.500 | 0.833 | 0.833 | 0.329 | 0.329 | 0.600 |
| **Retinal background changes** | 0.420 | 0.469 | 0.429 | 0.450 | 0.136 | 0.499 | 0.653 | 0.540 | 0.506 | 0.500 | 0.500 | 0.500 | 1.000 | 0.700 | 0.400 |

PT-Pre Treatment, R1-First review, R2-Second review

**Table 2:** Ocular Effects of Anti-Glaucoma Medications

## Hematological Assessment

The results of the Mixed Repeated Measures ANOVA showed no significant main effect of G6PD enzymopathy status on the haematological parameters after the overall use of anti-glaucoma medications as indicated in Table 3 with the exception of the Total and Indirect Bilirubin levels. These showed significant effect of the G6PD statuses with the full defects (cases) recording 6.689 ± 2.554μmol/l and 2.741 ± 1.035μmol/l increases for their Total and Indirect Bilirubin levels respectively than the No-defect subjects (controls).

| | Hb (g/dL) | RBC ($x10^{12}$/L) | HCT (%) | Total Bilirubin (µmol/l) | Direct Bilirubin (µmol/l) | Indirect Bilirubin (µmol/l) | IOP RE (µmol/l) | IOP LE (µmol/l) | BP Systolic (µmol/l) | BP Diastolic (µmol/l) |
|---|---|---|---|---|---|---|---|---|---|---|
| ***F*** | 0.092 | 0.356 | 0.26 | 3.457 | 2.506 | 3.594 | 0.659 | 1.065 | 0.613 | 2.420 |
| ***df*** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| ***Sig.*** | 0.912 | 0.702 | 0.772 | 0.038 | 0.091 | 0.034 | 0.521 | 0.351 | 0.545 | 0.098 |
| ***ηp2*** | 0.003 | 0.013 | 0.009 | 0.110 | 0.082 | 0.114 | 0.023 | 0.037 | 0.021 | 0.080 |

Hb – Haemoglobin level, RBC – Red Blood Cell count, HCT – Haematocrat level, IOP RE – Intraocular pressure Right eye, IOP LE - Intraocular pressure Left eye, BP – Blood pressure, F – F-Ratio, df – Degrees of freedom, Sig. – Significance level, ηp2 – Partial Eta Squared

**Table 3:** Overall anti-glaucoma effects among the G6PD statuses

Additionally, with the exception of Haemoglobin and Indirect Bilirubin parameters, no significant changes in the hematologic assessments were recorded after the overall use of anti-glaucoma medications ($p<0.05$) as indicated in Table 4. There was a drop in Haemoglobin level from 13.054 ± 0.453g/dL to 11.933 ± 0.370 g/dL during the first review and an increase to 12.074 ± 0.432 g/dL during the second review. Indirect bilirubin recorded a mean decrease from 5.557 ± 1.263g/dL to 3.960 ± 0.973 g/dL and 2.926 ± 0.521 g/dL during the first and second reviews respectively.

| | Hb (g/dL) | RBC ($x10^{12}$/L) | HCT (%) | Total Bilirubin (µmol/l) | Direct Bilirubin (µmol/l) | Indirect Bilirubin (µmol/l) | IOP RE (µmol/l) | IOP LE (µmol/l) | BP Systolic (µmol/l) | BP Diastolic (µmol/l) |
|---|---|---|---|---|---|---|---|---|---|---|
| **F** | 4.837 | 0.606 | .093 | 2.234 | 0.150 | 3.570 | 0.029 | 0.867 | 0.076 | 0.065 |
| **df** | 2 | 1.73 | 2 | 1.663 | 1.635 | 1.684 | 2 | 1.767 | 1.714 | 1.753 |
| **Sig.** | 0.010 | 0.525 | 0.911 | 0.122 | 0.818 | 0.039 | 0.971 | 0.412 | 0.902 | 0.917 |
| **ηp2** | 0.08 | 0.011 | 0.002 | 0.038 | 0.003 | 0.060 | 0.001 | 0.015 | 0.001 | 0.001 |

Hb – Haemoglobin level, RBC – Red Blood Cell count, HCT – Haematocrit level, IOP RE – Intraocular pressure Right eye, IOP LE - Intraocular pressure Left eye, BP – Blood pressure, F – F-Ratio, df – Degrees of freedom, Sig. – Significance level, ηp2 – Partial Eta Squared

**Table 4:** Overall Anti-Glaucoma Medications Effects During the Reviews

For the assessment of the individual anti-glaucoma medications effects, all but Timolol and Travaprost Brimonidine combination therapies recorded no significant main effect of G6PD enzymopathy status on the haematological parameters as indicated in Table 5. Timolol use recorded G6PD effect on haemoglobin levels with full defects having lesser haemoglobin levels in the study. Travaprost & Brimonidine experienced a higher serum bilirubin levels among the G6PD subjects (cases) than the controls.

| | Timolol | | | | Travaprost | | | | Timolol & Brimonid | | | | Timolol & Brinzolamide | | | | Travaprost & Acetazolamide | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***F*** | ***df*** | ***Sig.*** | ***ηp2*** | ***F*** | ***df*** | ***Sig.*** | ***ηp2*** | ***F*** | ***df*** | ***Sig.*** | ***ηp2*** | ***F*** | ***df*** | ***Sig.*** | ***ηp2*** | ***F*** | ***df*** | ***Sig.*** | ***ηp2*** |
| **Hb (g/dL)** | 5.841 | 2 | 0.014 | 0.455 | 0.077 | 1 | 0.789 | 0.009 | 2.324 | 2 | 0.144 | 0.297 | 0.241 | 1 | 0.672 | 0.108 | 0.021 | 1 | 0.895 | 0.007 |
| **RBC (x1012/L)** | 1.977 | 2 | 0.175 | 0.220 | 0.570 | 1 | 0.472 | 0.066 | 0.332 | 2 | 0.724 | 0.057 | 4.134 | 1 | 0.179 | 0.674 | 0.705 | 1 | 0.463 | 0.190 |
| **HCT (%)** | 2.832 | 2 | 0.093 | 0.288 | 0.106 | 1 | 0.753 | 0.013 | 2.004 | 2 | 0.181 | 0.267 | 0.919 | 1 | 0.439 | 0.315 | 0.075 | 1 | 0.801 | 0.025 |
| **Total Bilirubin (µmol/l)** | 0.049 | 2 | 0.952 | 0.007 | 0.367 | 1 | 0.561 | 0.044 | 7.061 | 2 | 0.011 | 0.562 | 1.366 | 1 | 0.363 | 0.406 | 0.109 | 1 | 0.763 | 0.035 |
| **Direct Bilirubin (µmol/l)** | 0.058 | 2 | 0.944 | 0.008 | 1.742 | 1 | 0.223 | 0.179 | 4.121 | 2 | 0.046 | 0.428 | 0.135 | 1 | 0.748 | 0.063 | 0.047 | 1 | 0.843 | 0.015 |
| **Indirect Bilirubin (µmol/l)** | 1.600 | 2 | 0.237 | 0.186 | 1.621 | 1 | 0.239 | 0.169 | 5.307 | 2 | 0.024 | 0.491 | 8.245 | 1 | 0.103 | 0.805 | 0.004 | 1 | 0.955 | 0.001 |
| **IOP RE (µmol/l)** | 0.517 | 2 | 0.607 | 0.069 | 0.451 | 1 | 0.521 | 0.053 | 0.596 | 2 | 0.548 | 0.098 | 2.819 | 1 | 0.235 | 0.585 | 0.011 | 1 | 0.923 | 0.004 |
| **IOP LE (µmol/l)** | 0.269 | 2 | 0.768 | 0.037 | 0.934 | 1 | 0.362 | 0.105 | 0.737 | 2 | 0.501 | 0.118 | 2.397 | 1 | 0.262 | 0.545 | 5.056 | 1 | 0.110 | 0.628 |
| **BP Systolic (µmol/l)** | 0.092 | 2 | 0.913 | 0.013 | 2.483 | 1 | 0.154 | 0.237 | 1.111 | 2 | 0.363 | 0.168 | 0.007 | 1 | 0.939 | 0.004 | 7.427 | 1 | 0.072 | 0.712 |
| **BP Diastolic (µmol/l)** | 1.344 | 2 | 0.293 | 0.161 | 8.450 | 1 | 0.020 | 0.514 | 0.398 | 2 | 0.681 | 0.068 | 13.964 | 1 | 0.065 | 0.875 | 0.054 | 1 | 0.831 | 0.018 |

Hb – Haemoglobin level, RBC – Red Blood Cell count, HCT – Haematocrat level, IOP RE – Intraocular pressure Right eye, IOP LE - Intraocular pressure Left eye, BP – Blood pressure, F – F-Ratio, df – Degrees of freedom, Sig. – Significance level, ηp2 – Partial Eta Squared

**Table 5:** Individual anti-glaucoma medication effect among the G6PD statuses

| | Timolol | | | | Travaprost | | | | Timolol & Brimonidine | | | | Timolol & Brinzolamide | | | | Travaprost & Acetazolamide | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *F* | *df* | *Sig.* | *ηp2* | *F* | *df* | *Sig.* | *ηp2* | *F* | *df* | *Sig.* | *ηp2* | *F* | *df* | *Sig.* | *ηp2* | *F* | *df* | *Sig.* | *ηp2* |
| **Hb (g/dL)** | 0.810 | 2 | 0.455 | 0.055 | 0.537 | 1.056 | 0.493 | 0.063 | 23.869 | 2 | 0.000 | 0.685 | 0.720 | 2 | 0.541 | 0.265 | 5.401 | 2 | 0.046 | 0.643 |
| **RBC (x1012/L)** | 0.132 | 1.075 | 0.740 | 0.009 | 2.097 | 1.062 | 0.184 | 0.208 | 15.639 | 1.354 | 0.001 | | 0.353 | 2 | 0.722 | 0.150 | 0.633 | 2 | 0.563 | 0.174 |
| **HCT (%)** | 1.055 | 2 | 0.362 | 0.070 | 3.112 | 1.098 | 0.111 | 0.280 | 1.297 | 2 | 0.293 | 0.105 | 3.453 | 2 | 0.135 | 0.633 | 0.939 | 2 | 0.442 | 0.238 |
| **Total Bilirubin (µmol/l)** | 0.985 | 2 | 0.386 | 0.066 | 6.260 | 2 | 0.010 | 0.439 | 1.453 | 2 | 0.256 | 0.117 | 1.020 | 2 | 0.439 | 0.338 | 5.023 | 2 | 0.052 | 0.626 |
| **Direct Bilirubin (µmol/l)** | 0.125 | 2 | 0.883 | 0.009 | 2.222 | 2 | 0.141 | 0.217 | 0.013 | 1.207 | 0.942 | 0.001 | 0.096 | 2 | 0.910 | 0.046 | 2.290 | 2 | 0.182 | 0.433 |
| **Indirect Bilirubin (µmol/l)** | 1.960 | 2 | 0.160 | 0.123 | 2.585 | 2 | 0.106 | 0.244 | 2.021 | 1.323 | 0.175 | 0.155 | 7.883 | 2 | 0.041 | 0.798 | 4.248 | 2 | 0.071 | 0.586 |
| **IOP RE (µmol/l)** | 1.35 | 1.277 | 0.779 | 0.010 | 0.218 | 2 | 0.807 | 0.027 | 0.929 | 2 | 0.410 | 0.078 | 4.769 | 2 | 0.087 | 0.705 | 1.538 | 2 | 0.289 | 0.339 |
| **IOP LE (µmol/l)** | 0.777 | 2 | 0.469 | 0.053 | 0.065 | 1.032 | 0.813 | 0.008 | 0.149 | 1.267 | 0.764 | 0.013 | 0.543 | 2 | 0.619 | 0.213 | 11.116 | 2 | 0.010 | 0.787 |
| **BP Systolic (µmol/l)** | 0.241 | 1.229 | 0.679 | 0.017 | 1.842 | 2 | 0.191 | 0.187 | 0.394 | 2 | 0.679 | 0.035 | 0.012 | 2 | 0.988 | 0.006 | 0.971 | 2 | 0.431 | 0.245 |
| **BP Diastolic (µmol/l)** | 0.297 | 2 | 0.746 | 0.021 | 0.405 | 2 | 0.674 | 0.048 | 0.674 | 2 | 0.520 | 0.058 | 0.117 | 2 | 0.897 | 0.055 | 0.430 | 2 | 0.669 | 0.125 |

Hb – Haemoglobin level, RBC – Red Blood Cell count, HCT – Haematocrat level, IOP RE – Intraocular pressure Right eye, IOP LE - Intraocular pressure Left eye, BP – Blood pressure, F – F-Ratio, df – Degrees of freedom, Sig. – Significance level, ηp2 – Partial Eta Squared

**Table 6:** Individual anti-glaucoma medication effect during the reviews

Also, with the exception of Timolol and Brimonidine combination drug, all the other anti-glaucoma medications recorded no significant changes in the hematologic assessments. Timolol and Brimonidine combination drug recorded 12.214 ± 0.469 g/dL to 11.905 ± 0.549 g/dL and to 11.500 ± 0.293 g/dL haemoglobin levels during the pre-treatment, first and second reviews respectively (Table 6).

## Intraocular and blood pressure assessment.

Mixed repeated measures ANOVA indicated no significant acute change in the intraocular and blood pressure findings among G6PD no defect subjects and full defect subjects during the pre-treatment, first reviews and second reviews for each of the anti-glaucoma medications used with the exception of Travaprost medication use (Table 5). Subjects who used Travaprost had a reduced diastolic BP from 75.000 ± 3.423mmHg to 71.875 ± 2.370mmHg and an increase to 74.375 ± 2.567mmHg during the second review.

## Discussion

Assessing drug safety among G6PD deficient glaucoma patients is essential in personalizing the care eye care practitioners render to patients to enhance safety.

In this research, the mean age of the subjects indicated that the majority of the glaucoma patients studied was in the geriatric population. This confirms the assertion in literature that aging is a major risk factor of glaucoma with the condition being more prevalent among the geriatric population [5].

The prevalence of G6PD deficiency recorded in this study confirms the prevalence rate indicated by the WHO for the Ghanaian populace [1]. Additionally, the prevalence of G6PD deficiency indicated in this study is comparable to the estimated G6PD enzymopathy prevalence rates among blood donors in Berekum, Ghana, [6] Osogbo, Osun State, Nigeria [7] and in Yasuj, Iran [8]. It is also comparable to the G6PD prevalence of 19% among patients at the OPD at Cape Coast Teaching Hospital [9]. In the absence of any known G6PD prevalence data among glaucoma patients, the prevalence found in this study is key in representing this special population. The high prevalence of G6PD enzymopathy among males could be attributed to it being X-linked recessive [2].

Investigation and analysis of possible acute drug adverse effects was performed using the 61 participants who reported for all three assessments during the study period of which 13 participants were having the G6PD enzymopathy. Drugs investigated included Timolol (a non-selective beta blocker), Travaprost (a prostaglandin analogue), Brimonidine (an adrenergic alpha-agonist), Brinzolamide (Topical carbonic anhydrase inhibitor) and Acetazolamide (Oral carbonic anhydrase inhibitor).

Conjunctival palor (yellowing) and redness are key ocular surface manifestation of hemolytic anemia and therefore any significant hemolysis associated with G6PD deficiency and drug interactions is likely to reveal these features [10]. However, none of the G6PD full defect participants experienced any of these for all the various drugs administered in the short term glaucoma management. Only few cases of conjunctiva injections were recorded which were even not associated with the G6PD statuses of the participants. The absence of conjunctival palor or yellowing indicated lack of pronounced hemolysis of the red blood cells with subsequent deposition of release bilirubin into the conjunctiva tissue.

Assessment of the posterior segment ocular tissues for hemorrhages, exudates, chorioretinal changes indicated no association between these ocular indicators and G6PD statuses of the participants for all the drugs taken. No account of retinal hemorrhages, a key ocular manifestation of hemolysis was recorded among all the subjects studied [11]. This indicated no significant acute adverse effects of all the antiglaucoma drugs administered among the G6PD deficient individuals since subtle changes indicated were not G6PD specific.

Additionally, evaluation of the intraocular and blood pressures indicated that Timolol caused no significant peculiar changes among the G6PD statuses. Similar findings were recorded among all the other anti-glaucoma medications taken with the exception of Travaprost which recorded an initial decrease in diastolic pressure during the first review and a subsequent increase in diastolic pressure during the second review. This indicates that all the anti-glaucoma drugs studied had no significant effect of the blood pressure system and the intraocular pressures.

This study therefore reveals that there is no peculiar acute ocular adverse effect associated with the use of anti-glaucoma medications among G6PD deficient individuals.

The cardinal drug-induced adverse effect among G6PD deficient individuals is hemolytic anemia. This causes depletion of the red blood cells resulting in a reduction in the red blood cells, hematocrit and haemoglobin levels and an increase in the serum bilirubin levels. In the study, no significant changes in the haemoglobin levels, red blood cells, and hematocrit and serum bilirubin levels were recorded among full G6PD deficient subjects (cases) after using the anti-glaucoma medications in general. This was comparable to findings from the no G6PD defective individuals (controls). The significant decrease in haemoglobin level during the first review from 13.054 ± 0.453g/dL to 11.933 ± 0.370 g/dL during the first review and subsequent increase to 12.074 ± 0.432 g/dL during the second review highlights the absence of any active hemolysis ongoing as confirmed by the decreased bilirubin levels recorded. The findings recorded were all within their respective normal ranges [12]. This is comparable to the individual anti-glaucoma drug effects recorded during the study.

This contradicts the assertion that, all forms of carbonic anhydrase inhibitors including Acetazolamide and Brinzolamide can potentially cause hemolysis when administered to G6PD deficient individuals [13]. This study however confirms findings of an in vitro study which stated that these carbonic anhydrase inhibitors rather produce a desirable effect of preventing hemolysis in G6PD deficient patients by acting as effective activators of the G6PD enzyme [4].

The prevalence of G6PD enzymopathy among the general populace is low [9] therefore limiting this study to a single eye care facility affected the number of G6PD cases recorded for the studies. Patients' willingness to partake in the studies was challenging since it required taking blood samples for G6PD enzymopathy investigation and haematological assessments which possess considerable ethical concerns.

Few haematological and serum bilirubin parameters recorded significant changes during their review assessments. However, the changes were inconsistent and not indicative of any onset of hemolytic anemia for all the anti-glaucoma medications taken (Table 5).

Future studies into the subject must be elaborated to increase the sample size significantly and patients given specific anti-glaucoma medications to increase the sample size of patients taking particular anti-glaucoma medications to enhance its external validity.

## Conclusion

From the study, no acute ocular and hematologic adverse effect(s) was established to be associated with the use of anti-glaucoma medications among G6PD deficient glaucoma patients. No clinical evidence was found to support the contraindication alert on the use of carbonic anhydrase inhibitors particularly Acetazolamide and Brinzolamide among G6PD deficient glaucoma patients. This calls for further confirmatory study to be conducted with a larger sample size to assess glaucoma chemotherapy among G6PD deficient glaucoma patients particularly the contraindication alerts flagged against the use of certain anti-glaucoma medications among G6PD deficient individuals.

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## Declaration of Interests

The authors declare no conflict of interest.

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