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# ASSESSING THE CLINICAL AND ETHICAL SIGNIFICANCE OF G6PD STATUS PRIOR TO PRIMAQUINE PRESCRIPTION FOR MALARIAL MANAGEMENT IN THE COMMUNITY HEALTH

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**G6PD Test, Primaquine, Hemolytic Anemia, Relapse Malaria, Standard guidelines.**

**Abstract**

*Primaquine is the widely used and presently the sole medication available for the obliteration of the recurrences of malaria caused by P.vivax and P. ovale because it is highly effective against latent malarial hypnozoites. Primaquine belongs to the class of 8-aminoquinoline drugs which is believed to act either by disrupting the Electron Transport Chain in parasite's mitochondria or via synthesizing the moieties of oxygen which are reactive and are involved in the destruction of parasites at cellular level. Primaquine is contraindicated in all those persons who are not tested for G6PD levels so while prescribing primaquine G6PD test is mandatory. The recommended regimen for safe usage of primaquine should eventually be adjusted according to the G6PD level of the patients. The objective of study is to evaluate the clinical as well as ethical significance of G6PD status prior to primaquine prescription for malarial management in the community health. The study was quantitative and cross sectional. The study primarily focused on whether International and National guidelines about Malarial Management are being followed in Hospitals during Malarial peak season. Two reliable and validated questionnaire were used for data collection. First questionnaire was designed for Health-care providers to track their responses about International and National Malarial Guidelines Management and the second questionnaire was particularly designed for patients to know their response whether they were properly guided about standard protocols followed worldwide. The assessment was made known to the participants, and they were asked to give their consent for participation. For the analysis of data SPSS; version.26 was used. We conducted our study on about 200 malarial patients who were prescribed Primaquine for radical cure to prevent relapse. A large chunk of patients were either in their early 20s or in the late 30s. Our study also included responses from 50 healthcare providers. Our goal was to assess clinical significance from health-care providers response and ethical significance from patients response. G6PD Status prior to Primaquine prescription is considered standard of care to avoid the risk*

*of Hemolytic Anemia but our study found that no such standards were being followed at all. Physicians were no longer going for G6PD screening for almost any patient. Training programs should be conducted and active participation of healthcare providers should be ensured about International and National Guidelines.*

## INTRODUCTION

### Primaquine: a pre-erythrocyte schizonticide:

Primaquine is the widely used and presently the sole medication available for the obliteration of the recurrences of malaria caused by P.vivax and P. ovale because it is highly effective against latent malarial hypnozoites. It also acts as gametocide against every form of malarial parasites, particularly P. falciparum. It is given via oral route and achieves peak plasma levels in 60-180 minutes. (1)

Primaquine belongs to the class of 8-aminoquinoline drugs which is believed to act either by disrupting the Electron Transport Chain in parasite's mitochondria or via synthesizing the moieties of oxygen which are reactive and are involved in the destruction of parasites at cellular level. Primaquine actuates intense haemolysis in people having deficiency with glucose-6-phosphate dehydrogenase (G6PD), a hereditarily X-connected disease. G6PD is a critical enzyme in RBC that interferes by producing the reduced NADPH (2)

Primaquine is contraindicated in all those persons who are not tested for G6PD levels so while prescribing primaquine G6PD test is mandatory. (3). It's contraindication protocols are recommended by the W.H.O for individuals who are G6PD deficient. It is also contraindicated in pregnancy because of it's chances for causing serious fetal health implications (4)

The recommended regimen for safe usage of primaquine should eventually be adjusted according to the G6PD level of the patients. Guidelines strictly suggest the testing for enzyme status of patients prior administration of primaquine. Therefore, primaquine is generally given without earlier G6PD testing - in this way presenting infected individuals prone to haemolytic pallor - or isn't regulated - presenting individuals with significant chances for revert of fever, including repeated chills, spread and asset restricted settings. (5)

### Glucose-6-phosphate dehydrogenase and it's deficiency:

Glucose-6-Phosphate dehydrogenase (G6PD) is a biocatalyst in Hexose Mono Phosphate Shunt that performs an essential task in guarding the RBCs from oxidant damage. (6) G6PD deficiency is genetic disorder seen in majority of the people of the world. It's core cause is genetics in which mutations in the gene coding for G6PD enzyme has been studied. Individuals with G6PD deficiency usually do not show any symptoms but hemolytic anemia can be caused which is triggered with certain drugs such as, primaquine (absolute risk), sulpha drugs, nitrofuranotin, dapsone and phenazopyridine. Other common triggers are infections and broad beans, naphthalene. (7)

### Prevalence of Glucose-6-phosphate dehydrogenase deficiency:

This condition is generally pervasive. It has affected about three hundred and fifty million people worldwide, with it's 3-35% prevalence data in tropical zones. Radical cure requires an augmented course of primaquine usually 2 weeks with the total dose of 3.5 -7mg/kg. For reduction of transmission previously a single dose of 0.75mg/kg is recommended which is now decreased to 0.25mg/kg. (8) G6PD deficiency prevalence in Pakistan is 7-8.6% in Peshawar, 6.2-7.5% in Karachi, 4.3-4.8% in Rawalpindi, 2.5% in Lahore, and 3.4% in Malakand. A study conducted by Aga Khan University in 2013 suggested that Pashtun population in Pakistan is highly prevalent to this enzyme deficiency because of their genetic make-up. (9,10)

Primaquine treatment comes with several risks, including the potential for hemolysis. Additionally, it can cause prolongation of QT. Therefore, it's important to avoid using primaquine alongside other medications that also extend the QT interval, especially in patients with existing heart conditions like ventricular arrhythmias, decreased heartbeat, or long QT interval. (11)

Persons with a G6PD deficiency (20 per cent) or a moderate deficiency (20–45 per cent) are more prone to hemolysis when treated with a standard dose (14 days a day), but have demonstrated tolerance to a

prolonged therapy with a single dose per week for eight weeks. (12) By using the reflectometry evaluations, both G6PD activities and hemoglobin levels are checked from the recently drawn blood sample. (13)

**Biochemical pathway:**
The committed step in hexose monophosphate (HMP) shunt is catalyzed by glucose-6-phosphate dehydrogenase, in which nicotinamide adenine dinucleotide phosphate (NADP+) gain electrons to form nicotinamide adenine dinucleotide phosphate (NADPH) and changes glucose-6-phosphate to 6-phosphogluconolactone. (14) In order to sustain glutathione within its reduced form (also known as G SH), NADPH operates as an important reducing agent in biosynthesis. The primary antioxidant within the cell is reduced glutathione, which breaks down organic and hydrogen peroxides through processes driven by glutathione peroxidase. (15) The pathway guards red blood cells from oxidative damage. If G6PD activity drops below about 30 percent of normal levels, NADPH and reduced glutathione production become inadequate, making cells vulnerable during oxidative stress. (16)
The risk and benefit of primaquine must be thoroughly considered, mainly when it is not tested for G6PD. This also includes deciding when to perform G6PD testing, particularly in nations where low G6PD status is common. The valuation should include both qualitative and quantitative methods for testing G6PD, and it`s significant to know the preferred features of qualitative testing that are most suitable for use at local health facilities. So there needs to be a plan to organize and carry out G6PD testing throughout the country so that the results are the consistent and trustworthy everywhere. (17)

**Rationale for the G6PD Testing:**
G6PD testing facilitates safe application of primaquine in P. vivax malaria, decreasing and obviating haemolytic anemia in G6PD deficit individuals. This enhances patient outcomes and decreases the onus of health care. (18)

**Statement of the Problem:**
Complete negligence of G6PD Testing while Primaquine Prescription makes patient prone to risk of Acute Haemolytic Anaemia and raises a concern on Effective Malarial Management guidelines.

**RESEARCH METHODOLOGY:**
• Study Design:
The study was quantitative with Positivist research philosophy and Deductive Reasoning as approach. The time-horizon of the study was cross-sectional. It primarily focused on whether International and National guidelines about Malarial Management are being followed in Hospitals during Malarial peak season.
• Study Setting and Participants:
The study was conducted at Chandka Hospital Larkana and patients admitted at the Hospital and Healthcare providers jointly participated in our study.
• Sample size:
The rational size of sample was 200 malarial patients admitted at the Hospital and 50 Health-care professionals who were looking after and providing their services to the admitted patients. Sample was collected in September 2024 during the peak Malarial season.
• Duration of Study:
The duration of study was 3 months.
• Ethical Considerations
Approval was formally taken by Hospital Administration on the condition that privacy and secrecy of patients and healthcare providers would be fully respected.
• Inclusion Criteria:
Malarial patients of all ages and gender.
• Exclusion Criteria:
Infants and Pregnant women.
• Data Collection:
Two reliable and validated questionnaire were used for data collection. First questionnaire was designed for Health-care providers to track their responses about International and National Malarial Guidelines

Management and the second questionnaire was particularly designed for patients to know their responses whether they were properly guided about standard patient-care protocols followed worldwide.

• Statistical Analysis:

For the analysis of data SPSS; version.26 was used.

**DATA-ANALYSIS:**

We conducted our study on about 200 malarial patients who were prescribed Primaquine for radical cure to prevent relapse. Our study included patients from each and every age group ranging from 12-60 years; with people in their early 20s and late 30s constituted the majority. About 80% of the participants were Male and Female constituted about 20% of the sample population.

We extended the boundary of our study and included about 50 health-care providers' responses to assess the clinical relevance and significance of the G6PD test. Health care providers were categorized on the hierarchical basis starting from HOD levels to the House-physicians and based on their experiences and exposures to the health care system. Each hierarchical position was given equal and fair chance to record their response.

**DESCRIPTIVE STATISTCS OF PATIENTS:**

**Table No:1 Gender**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | | 1 | .5 | .5 | .5 |
| | F | 40 | 20.0 | 20.0 | 20.5 |
| | M | 159 | 79.5 | 79.5 | 100.0 |
| | Total | 200 | 100.0 | 100.0 | |

**Table No:2 Did Doctor consult them to go for G6PD test before taking primaquine?**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | No | 200 | 100.0 | 100.0 | 100.0 |

**Table No:*3* Did they experience change in the skin or urine colour after Primaquine?**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | ano | 1 | .5 | .5 | .5 |
| | No | 183 | 91.5 | 91.5 | 92.0 |
| | Yes | 16 | 8.0 | 8.0 | 100.0 |
| | Total | 200 | 100.0 | 100.0 | |

**Table No:4 Did they find this unethical that their health & life is being compromised?**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | | 1 | .5 | .5 | .5 |
| | No | 149 | 74.5 | 74.5 | 75.0 |
| | Yes | 50 | 25.0 | 25.0 | 100.0 |
| | Total | 200 | 100.0 | 100.0 | |

**Table No:5 Did they consider that this will create trust-deficit towards healthcare community?**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | No | 159 | 79.5 | 79.5 | 79.5 |
| | Yes | 41 | 20.5 | 20.5 | 100.0 |
| | Total | 200 | 100.0 | 100.0 | |

**Table No:6 Did this negligence derail the malarial elimination program?**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | | 1 | .5 | .5 | .5 |
| | No | 144 | 72.0 | 72.0 | 72.5 |
| | Yes | 55 | 27.5 | 27.5 | 100.0 |
| | Total | 200 | 100.0 | 100.0 | |

**Cross-tabulation:**
Did they find this unethical that their health and life is being compromised? Did this negligence eliminate malarial elimination programme?

**Chi-Square Tests**

| SS | Value | df | Asymptotic Significance (2-sided) |
|---|---|---|---|
| Pearson Chi-Square | 272.130[a] | 4 | .000 |
| Likelihood Ratio | 80.087 | 4 | .000 |
| N of Valid Cases | 200 | | |

a. 5 cells (55.6%) have expected count less than 5. The minimum expected count is .01.

**DESCRIPTIVE STATISTICS OF HEALTH-CARE PROVIDERS:**

**Table No: 1 Rank/Position**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| **Valid** | **Consultant** | **6** | **12.0** | **12.0** | **12.0** |
| | House Officer | 10 | 20.0 | 20.0 | 32.0 |
| | Medical Officer | 14 | 28.0 | 28.0 | 60.0 |
| | Resident | 15 | 30.0 | 30.0 | 90.0 |
| | Senior Physician (HOD) | 5 | 10.0 | 10.0 | 100.0 |
| | Total | 50 | 100.0 | 100.0 | |

**Table No:2 Did they order G6PD test before prescribing primaquine in malaria patients?**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | No | 50 | 100.0 | 100.0 | 100.0 |

**Table No:3 Were they aware that primaquine carries the risk of acute haemolytic anemia in G6PD deficient patients?**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | Yes | 50 | 100.0 | 100.0 | 100.0 |

**Table No:4 Were they informed that G6PD testing before primaquine prescription is mandatory a/c to W.H.O guidelines?**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | No | 23 | 46.0 | 46.0 | 46.0 |
| | Yes | 27 | 54.0 | 54.0 | 100.0 |
| | Total | 50 | 100.0 | 100.0 | |

**Table No:5 What were the main factors of negligence or not obeying the standard guidelines?**

| | | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Valid | Can monitor patients if emergency happens and save life (early monitoring). | 1 | 2.0 | 2.0 | 2.0 |
| | Common misconception that Low-Dose Primaquines are safe to administer without G6PD test. | 11 | 22.0 | 22.0 | 24.0 |
| | Lack of awareness about guidelines. | 9 | 18.0 | 18.0 | 42.0 |
| | Less G6PDD prevalence in our population. | 14 | 28.0 | 28.0 | 70.0 |
| | Operational pressures of rapid malarial management as their main priority over G6PD Testing. | 15 | 30.0 | 30.0 | 100.0 |
| | Total | 50 | 100.0 | 100.0 | |

**Cross-tabulation:**
Were they informed that G6PD Testing before primaquine prescription is mandatory according to WHO Guidelines?
What were the main factors of negligence or not obeying the standard guidelines?

**Chi-Square Tests**

| | Value | df | Asymptotic Significance (2-sided) |
|---|---|---|---|
| Pearson Chi-Square | 17.822[a] | 4 | .001 |
| Likelihood Ratio | 22.363 | 4 | .000 |
| N of Valid Cases | 50 | | |

a. 4 cells (40.0%) have expected count less than 5. The minimum expected count is .46.

**DISCUSSION:**

Although it is standard recommendation to go for G6PD status prior to Primaquine prescription, findings of our study were contrary to the standard protocols. There was clear discrepancy between Standard Guidelines and clinical practice which would have serious implications for the public health. The absence of standardized screening generally pre-disposes the patients to inevitable risks of severe hemolysis, paleness, jaundice and acute kidney injury.

Failure to screen for G6PD status also undermines the effectiveness of malaria elimination strategies and further leads to increased morbidity, reduced adherence and public's trust deficit in the healthcare system. It also raises ethical concerns that patients are being put at the risk of a clinical emergency due to negligence.

Firstly, small sample size and secondly lack of patient follow-up days-weeks after the incidence of hemolysis would be the main limitations of our study but findings are evidently strong enough to suggest that a clear gap exists between the current clinical practices and standard guidelines which could have substantial effects on the community health.

**CONCLUSION:**

G6PD Status prior to Primaquine prescription is considered standard of care to avoid the risk of Hemolytic Anemia but our study found that no such standards were being followed at all. Physicians were no longer going for G6PD screening for almost any patient.

Findings have shown that reasons for the breach of these protocols were not linked to the availability of resources (test kits) but lack of awareness about guidelines among health-care providers, large number of hospitals re-admission rate and Health system's priority of rapid malarial management over enzymatic testing due to operational pressures, under-estimation of G6PD Deficiency prevalence in their population and misconception that low dose primaquine regimens are generally safe to administer regardless of the G6PD status.

Protecting patients from one condition and putting them at the risk of another life-threatening condition shows a serious lapse in the healthcare system and raises question about the patient compliance.

Whereas, findings from patients response suggest that not a single patient was screened for G6PD test regardless of their background, existing medical condition or the symptoms of blood-related disorders. Patients' responses clearly conclude this highly unethical and disappointing that they were not consulted about the significance of this test and the possible consequences of the negligence on their health and labelled it as a mal-practice, they further added that this will negatively impact malarial elimination strategies and will create trust-deficit towards healthcare system as a whole.

Now-a-days patient gets more safety information when buying biscuits than from the healthcare provider about the health and well-being; one patient taunted.

**RECOMMENDATIONS:**

Based on the study, these are the suggestions which should be adapted:

• Training programs should be conducted and active participation of healthcare providers should be ensured about International and National Guidelines on Malarial Management.

• Sense of Responsibility and Realization must be promoted among Clinicians to fill the gap between International guidelines and Clinical practice.

• Electronic Health Record Systems should be installed that would give an easy access to patients medical records and ensures to prevent primaquine prescription until G6PD test results are confirmed.

• Community health should be prioritized over operational resources.

• Public Advertisements must be made by the Government about the safe and precautionary usage of drugs for Malarial Management in the endemic regions.

• Citizen awareness campaigns must be run to cultivate the civic sense among people about the risks around their health.

• Caution must be exercised.

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