Original Research Article

SAFETY OF WEEKLY PRIMAQUINE IN GLUCOSE 6 PHOSPHATASE DEHYDROGENASE (G6PD) DEFICIENT CHILDREN

ABSTRACT

Aim: To assess the Safety of weekly Primaquine in Glucose 6 Phosphatase Dehydrogenase (G6PD) deficient children, for radical treatment of plasmodium vivax malaria

Study Design: cross sectional study

Place and duration: Pediatrics Out Patient Department, Liaquat University of Medical and Health Sciences Hyderabad from 11 January 2018 to 31st August 2019 (total 20 months' duration)

Methodology: A sample of 40 patients was studied during study period. Male children between 4 years to 12 years of age having confirmed vivax malaria were included in the study. If G6PD result showed decreased level of G6PD level then, they were enrolled for study. Treatment was given with Artemether and Lumefantrine for 3 days while Primaquine, 0 .75 mg base/kg body weights once a week was given for 8 weeks. Patients were followed at OPD initially on 3rd day of therapy then every week for 8 weeks for any hemolysis.

Result: There was no hemolysis during the first week and 8 weeks after therapy. Most common side effect was abdominal pain 4 (10%). Mean hemoglobin was 11.8mg/dl. Plasmodium Vivax was negative on 3rd day of therapy, it was also negative on 8 week of therapy.

Conclusion: Primaquine 0.75mg//kg/week for total eight weeks is highly effective for the radical cure of Plasmodium Vivax in G6PD deficient children. There is no recurrence of plasmodium

vivax after 8 weeks of therapy. We found this regimen safe as there was no hemolysis demonstrated in children.

Key Words: Malaria, Plasmodium Vivax, G6PD Deficiency, Hemolysis, Radical Cure

Introduction:

Malaria is almost eradicated from developed nations, but continues a health problem in a substantial part of the world. Malaria is a major health issue in Asian and African countries. About 50% of the world's population lives in malaria endemic countries. [1]

About 1 million deaths occur each year due to malaria and most of them are young children. In malaria endemic countries it may cause 10% of all deaths in children. In Pakistan about 1.6 million cases of malaria occurs per year including 300 000 confirmed cases in public health-sector.[2]

The goals of antimalarial treatment in P. vivax are to treat the malaria and to prevent the relapse of malaria. This cannot be achieved by a single drug so a combination of antimalarial is required to achieve the goal. [3] In chloroquine (CQ) sensitive regions, the WHO recommends 3 days of CQ therapy or an artemisinin combination therapy plus 2 weeks of PQ (provided the person is not G6PD deficient). [4]

Primaquine induces dose-dependent acute hemolytic anaemia in individuals with G6PD deficiency, a genetically X-linked disorder [5]. This condition is widely prevalent affecting over 400 million people globally, with a prevalence of 3–35% in tropical areas [6]. Global prevalence of G6PD deficiency is 4.5% and 1.8% in Pakistan.[7]

Often the facility of G6PD testing is not available at points of care after a diagnosis of P. vivax malaria. As a result, Primaquine is usually given without prior G6PD testing, thus exposing vulnerable patients to the risk for hemolytic anemia. On the other hand, where it is not

administered exposes patients to the risk for repeated relapses of P. vivax malaria, with consequent morbidity and transmission. For the elimination of P. vivax liver-stage infections (radical cure), Primaquine is given with dose, 0.25mg base/kg/ body weight daily (3.5 mg/kg total dose) for 14 days, in addition to the antimalarial medicine that cures the blood-stage infection. [8] In a significant proportion of G6PD-deficient patients, however, the 14-day regimen of Primaquine induces dose-dependent, potentially severe hemolysis [9]. Instead of daily Primaquine they should receive once weekly Primaquine 0.75 mg/kg for 8 weeks. [10]
The rationale of this study was to assess whether once a week for total eight week PQ regimen is effective at radical cure without the associated risk of hemolysis in G6PD deficient children. This regimen may be appropriate for poor countries where G6PD testing is unavailable. The objective of this study was to assess the safety of weekly Primaquine given to G6PD deficient persons, for the radical treatment of Plasmodium Vivax Malaria.

Methodology

Hemolysis is defined as destruction of Red Blood Cells leading to pallor, jaundice and red urine. G6PD level < 50 percent of normal is labelled as G6PD deficiency[11]. This cross sectional study was conducted at Pediatrics Out Door Department, Liaquat University of Medical and Health Sciences Hyderabad from January 2018 to August 2019 (total 20 months' duration). Approval was taken from Ethical Review Committee of University. As no universal guidelines are available regrading dose of Primaquine in G6PD deficient patients[5], the parameter required to calculate sample size are not available, a sample of 40 patients was studied during study duration. Male children between 4 years to 12 years of age were included in the study. Patients living >100 kilo meter away from the Civil Hospital Hyderabad were excluded from the study due to the concern of delayed management in case of hemolysis .Person who fulfilled the

inclusion criteria were registered for the study. The informed consent was taken from the parents.

At pediatric Out Patient Department Hyderabad, children are checked for malarial parasite by doing MP test. Children with fever are classified as clinical suspected malaria according to IMNCI protocols are also checked for malarial parasite. Blood is taken with finger prick on a glass slide and is checked for the presence or absence of malarial parasites. In whom, who are positive for plasmodium vivax parasite, 2 ml blood was taken from the vein at the dorsum of right hand and was sent for G6PD level. Blood was also checked for Complete blood count, Reticulocyte count, Liver function test and creatinine. Quantitative testing of G6PD activity was checked at LUMHS Research Laboratory by using spectrophotometric assay and functioning cold chain was maintained. If G6PD result showed decreased level of G6PD level then, they were enrolled for study.

After enrolment they were treated with Artemether and Lumefantrine for 3 days while Primaquine, 0 .75 mg base/kg body weights was given once a week for 8 weeks. Patients were followed at OPD initially on 3rd day of therapy then every week for 8 weeks. Patients were informed about the risk for acute hemolytic anaemia when taking Primaquine. They were instructed to monitor the colour of their urine and to stop taking Primaquine if their urine becomes dark and give oral hydration and shift the patient to hospital, where patient will be admitted. Patients were taken from the area that is within 100 Kilometer area near to Civil Hospital Hyderabad as they can reach the hospital within 1 hour in case of hemolysis. Clinical assessment will be done and blood will be sent to laboratory to check haemoglobin or hematocrit, serum creatinine or urea (blood urea nitrogen). Blood will be transfused if Haemoglobin is < 7 g/dL or Haemoglobin is between 7 to 9 g/dL with concurrent hemolysis. If

the Haemoglobin is > 9 or 7–9 g/dL and no evidence of concurrent hemolysis, then careful fluid management with monitoring of urine colour will be done. At weekly checkup we checked for fever and jaundice and asked for vomiting, abdominal pain, dizziness, breathlessness and color of urine. Compliance of Primaquine was also ensured. In case of Hemolysis, Primaquine was stopped and Hb level checked and managed accordingly.

The data was analyzed by using SPSS version 22.0. Categorical variables like: gender, complications, and outcome were analyzed by applying Chai Sq. Test and numerical values were measured in mean and frequency.

Result:

In this study total 40 children having G6PD deficiency were treated with Artemether and Lumefantrine while radical therapy was done with weekly dose of Primaquine for 8 weeks. The demographic parameters are mentioned in table 1. Plasmodium Vivax was negative on 3rd day of therapy, it was also negative on 8 week of therapy. (Table 2). Response to therapy and any adverse effect was monitored. There was no hemolysis during the first week and 8 weeks after therapy. Most common side effect was abdominal pain 4 (10%), other side effects are mentioned in table 3. Mean hemoglobin was 11.8, while the rest of biochemical factors are mentioned in table 4.

Table 1: Demographic Parameters of Study Participants (n=40)

Characteristic	**Number**	**Percentage**
Age (Years)		
5-8	18	45

9-12	22	55
Weight (Kg)		
15-25	19	47.5
26-40	18	45
>40	3	7.5

Table 2: Mean Value of hemoglobin concentration and Vivax Status in G6PD deficient children after giving Primaquine (n=40)

Day of Primaquine	**Mean Hb (mg/dl)**

1	11.6
3	11.4
7	11.1
Plasmodium Vivax +ve	
Day 3	No
Day 7	No
Week 8	No

Table 3: Number of subject adversely affected after Primaquine Therapy (n=40)

Symptoms	**Day 1 n (%)**	**Day 3 n (%)**	**Day 7 n (%)**	**Week 8 n (%)**
Pallor	1 (2.5)	1 (2.5)	1 (2.5)	0 (0)

Bleeding	0 (0)	0 (0)	0 (0)	0 (0)
Edema	0 (0)	0 (0)	0 (0)	0 (0)
Jaundice	3 (7.5)	3 (7.5)	3 (7.5)	0 (0)
Respiratory Difficulty	1 (2.5)	0 (0)	0 (0)	0 (0)
Abdominal Pain	4 (10)	4 (10)	0 (0)	0 (0)
Hepatomegaly	3 (7.5)	3 (7.5)	3 (7.5)	0 (0)
Splenomegaly	3 (7.5)	3 (7.5)	3 (7.5)	0 (0)
Low Back Pain	0 (0)	0 (0)	0 (0)	0 (0)

Table 4: Mean of Hematological and Biochemical Parameters in G6PD Deficient patients after taking Primaquine (n=40)

Parameters	**Day 3**	**Day 7**
Total Bilirubin (mg/dl)	1.3	1.5

ALT	35	40
AST	32	33
Hemoglobin (g/dl)	11.8	12.00
Hematocrit (%)	35.2	35.8
Reticulocyte (%)	1.8	2.1
Creatinine (mg/dl)	1.1	0.9

Discussion:

The malaria endemic countries where G6PD testing is not available have adopted 0.75mg/kg/week (total 8 weeks) protocol for the radical cure of vivax malaria. As this regimen is useful for G6PDd A- variant (less severe form) so there is need of improvement in radical cure

policies and practice. In this study 100% case of plasmodium vivax were cured by giving Artemether and Lumefantrine combination therapy. On day three of treatment all cases had negative MP test. There was no hemolysis noted during eight weeks of treatment with Primaquine. Minor side effects like abdominal and hepatomegaly was noted in few children. There was no significant change in hemoglobin concentration during the study period.

In a recent study PQ ≤ 2.5 mg base/kg was associated with 25% chance of recurrence at 4–6 months, compared with 6.7% chance when > 2.5 mg/kg to < 5.0 mg/kg) was given. > 5.0 mg/kg were associated with a recurrence rate of 0% at 1 month. [12] In other two studies there was high effectiveness of >5mg/kg PQ compared with a control arm. [13, 14]

There are different policies for the Radical cure of vivax with Primaquine across the Asian region. Some are checking G6PD level before Primaquine administration, although in practice mostly this is not applicable. In a study from Cambodia Primaquine was given (0.75 mg/kg PQ dose weekly for 8 weeks) to G6PD deficiency persons. There was no significant hemolysis noted during the total eight weeks of treatment. [15]

Although G6PD testing is advised by various countries but it is not available most of the time, that's why physicians decision play an important role in decision making. [16]

The use of Primaquine in private sector is conflicting, in some countries there is very little use while in others it is the main source of antimalarial treatment. [17]. In an Indian study the relapse rate was 0% with the 14-day regimen, 26.7% with the 5-day, and 11.7% when no Primaquine treatment was given. [18], [19] According to Chu et al Primaquine 0.5mg/kg for 14 days was well tolerated as compared to 1mg/kg for 14 days causing hemolysis. [20]

According to a study done at Northern Pakistan the prevalence of G6PD deficiency is 2-8% and G6PD Med is the most frequent variant [21]. Primaquine causes serious hemolysis in persons

having G6PD Med deficiency [22]. In Pakistan Primaquine administration needs mandatory G6PD testing although this test is not widely available. A study from the southern Pakistan showed that out of 200 participants 6 were G6PD deficient [23]. Recurrent jaundice due to hemolytic anemia can occur in G6PD deficient people. In a local study G6PD deficiency was detected in 1.8% people, 1.07% in Kashmiris, 1.47% in Punjabis, 2.77% in Sindhis, and 3.17% in Pathans. About 5.7% persons had the history of recurrent jaundice [24]. A 14-day course of Primaquine (PQ) can cause severe hemolysis in G6PD deficient persons and the testing for G6PD is seldom available enforcing the need of safe dose of PQ without G6PD testing.

A study from Pakistan concluded that the 8-week PQ course is more effective in preventing relapse and widespread use of this regimen could make an important contribution [25]. A 5-day course of PQ for vivax malaria is used commonly in South Asia to reduce the risk of hemolysis [26]. Studies from Pakistan and India showed that the 5-day PQ regimen is ineffective in reducing relapses [27, 28]. The 14-day course of Primaquine is only recommended where the G6PD status of the individual is known [29]. That's why Primaquine is less frequently used as G6PD testing is not available in developing countries. This regimen was ineffective in Pakistan and India, because of frequent relapse rates. [30]. As compared to 15 days course of Primaquine, 8 weeks course was found more effective in a local study [31].

In Asian countries there are different policies for Primaquine use. In some countries G6PD testing is required before the administration of Primaquine. Pakistan follows this protocol but mostly G6PD testing is not available. In Myanmar this facility is lacking in villages and they are using weekly Primaquine for total 8 weeks. This regimen is also followed in Iran

In Pakistan there is reluctance and low prescription for Primaquine by Pediatricians and physicians due to their concern of hemolysis in G6PD deficiency children. A local study from

Karachi showed that Primaquine was prescribed as prophylaxis to prevent relapse in only 6.2% of cases infected with P. vivax [32].

Conclusion: Primaquine 0.75mg//kg/week for total eight weeks is highly effective for the radical cure of Plasmodium Vivax in G6PD deficient children. There is no recurrence of plasmodium vivax after 8 weeks of therapy. We found this regimen safe as there was no hemolysis demonstrated in children. This regimen can be safely used in children who has plasmodium vivax and whose G6PD level cannot be determined.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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