POST-OPERATIVE AUDIT OF G6PD-DEFICIENT MALE CHILDREN WITH OBSTRUCTIVE ADENOTONSILLAR ENLARGEMENT AT UNIVERSITY COLLEGE HOSPITAL, IBADAN, NIGERIA.

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Abstract

Background: *G6PD deficiency ranks among the commonest hereditary enzyme deficiency worldwide and notable as a predisposing condition to haemolyticcrises. The fear of possible untoward effects is often expressed by parents of G6PD deficient male children scheduled for surgery after obtaining an informed and understood consent. The parental perception of obstructive adenotonsillar enlargement in this condition was also appraised.*

Methods: *A retrospective chart review of all G6PD deficient male children between ages 1 to 7years who had adenotonsillectomy over a 3year period at University college Hospital, Ibadan, Nigeria.*

Results: *The patients comprised of 22 G6PD deficient male children diagnosed shortly after birth upon development of neonatal jaundice. Fifteen(68.2%) and 6(27.3%) of the patients subsequently developed episodes of drug- induced haemolysis and non-haemolytic drug reactions prior to undergoing adenotonsillectomy by the otolaryngologists. None of the patients was observed to develop haemolytic crises up to 2weeks post-adenotonsillectomy. From the parental perception and responses in the follow-up period,all 22(100%) patient had resolution of noisy breathing, 20(91%) had improvement of snoring and apnoeic spells. Only 15 (68%) were reported to stop mouth-breathing.*

Conclusion: *The small sample size and lack of assay of serum bilirubin level to determine microscopic haemolysis were reckoned as limitations to the study. The study did not find any case of critical post-anaesthetic or post-operative event. Hence, the benefit derived from the surgeries outweighs the risk of drug-induced hemolysis entertained by both the parents and health-care givers.*

Key words: *Post-operative audit, Glucose-6-phosphate deficiency,obstructive adenotonsillar enlargement.*

Introduction

Globally, adenotonsillectomy is arguably the most performed surgery by the paediatric otolaryngologist[1].From the multitude of complaints, the indication for this surgery isfrequently due to obstructive adenotonsillar enlargement. Unlike normal children with no genetic abnormality, surgery for children having obstructive adenotonsillar enlargement and confirmed to have genetic abnormality requires thorough evaluation and extreme caution due to the attendant sequelae from surgery or anaesthetic agents. Often times,surgery becomes necessary when there is significant impairment of quality of life despite medical treatment. A subset of children with obstructive adenotonsillar enlargement attending ENT out-patient clinic are found to be Glucose -6 -phosphate dehydrogenase deficient. This condition is said to be commoner in male children and prevalent in Africans. The obstructive adenotonsillar disease predisposes them to problems of noisy breathing, snoring,nasal blockage,mucoid nasal discharge, mouth breathing, frequent apnoeic spells, day time hyper-somnolence and failure to thrive. Every health care-giver involve in paediatric care needs to be conversant with the problems of G6PD deficiency and exercise great caution in the management of a G6PD deficient male child. Infective and inflammatory conditions are known to be the leading cause of haemolytic crises in G6PD deficient patients[2,3]. Similarly, some peri-operative drugs and anaestheticagents mayproduce haemolysis effect in G6PD deficient patients when the G6PD deficient cells are subjected to metabolic oxidative stress which may overwhelm red blood cell metabolism of NADPH. The drugs that precipitate haemolysis in these G6PD deficient red cells interact with the haemoglobin and oxygen, leading to intracellular formation of hydrogen

peroxide (H_20_2) and oxidizing radicals. The accumulated radicals in the red cells oxidize the haemoglobin and other proteins leading to loss of cell function and death. Consequently, the patient develops haemolyticcrises which may be self-limiting if not very severe or can lead to permanent neurological damage or death[4,5].

G6PD deficiency is the most common hereditary enzyme deficiency which affects approximately 400million people worldwide[6] and is distributed in areas of current and previous endemic malaria[7]. This human enzyme defect is caused by mutation in the G6PD gene located on chromosome Xq28; thus, transmission of genetic defect is X-linked. Hemi zygote males are most affected and homozygous females least affected; both are prone to red cell hemolysis. Heterozygote females have mixed G6PD normal and deficient red cells and their susceptibility to hemolysis depends on the balance between expression of the normal and abnormal X chromosomes[8].The highest frequencies are detected in Africa, south East Asia , Central and Southern pacific islands, the Mediterranean regions, and in the Middle East[4].There are some 140 different genotypes of G6PD deficiencies[9] with corresponding enzyme activity phenotypes that vary from mild to severe.

Since 1979, the fluorescent qualitative spot test has been recommended as the most suitable method of screening G6PD deficiency in the field despite the need for an UV lamp, water bath incubator and micropipette. On the other hand, the diagnosis of G6PD deficiency may be done by a variety of quantitative spectrophotometric enzyme activity assays or DNA based detection of specific mutations[10,11].

G6PD is an enzyme that catalyzes the first step in pentose phosphate pathway (PPP)[12].The pentose phosphate pathway include converting glucose to ribose-5-phosphate, a precursor to RNA, DNA, ATP, CoA, NAD and FAD. The NADPH generated in the pathway provides the reducing energy of the cell by maintaining the reduced glutathione within the cell. The reduced glutathione function as an anti-oxidant and protects cells against oxidative damage[12]. The red blood cells in G6PD patient are unable to scavenge free radicals produced by oxidative stress thereby predisposing the cells to haemolysis. Unlike other cells,RBC do not have the alternative NADPH-producing metabolic pathways, making them especially susceptible to oxidative stress, resulting in haemolytic anaemia.

The factor responsible for accelerated destruction of G6PD deficient red cells during infections is unknown. One possible explanation is that red cells are damaged by oxidants generated by phagocytosing macrophages, a mechanism similar to that seen in drug-induced haemolysis[2,13]. Certain metabolic conditions, such as diabetic acidosis also appears to be capable of triggering destruction of G6PD-deficient red cells. Metabolic responses to surgical trauma leading to acidosis and hyperglycaemia are potential precipitating factors[14] and correction of the abnormalities is associated with reversal of the haemolytic process.

Post-operatively, the G6PD deficient patient can present certain clinical manifestation that may trigger the need for additional support or treatment. In general, haemolysis is seen in 1 to 3 days after contact with the trigger factors. Acute haemolysis is self-limiting, but in rare instances it can be severe enough to warrant a blood transfusion[15]. The patient may develop cyanosis, headache, fatigue, tachycardia, dyspnoea, lethargy, lumbar or substernal pain, abdominal pain, splenomegaly, haemoglobinuria and/or scleral icterus[4,14,16]. The breakdown products of haemoglobin accumulate in blood, causing jaundice and may be excreted in urine, making it dark brown.

The World Health Organization has classified the different G6PD variants according to the magnitude of the enzyme deficiency and severity of haemolysis. **Class I** variant have severe enzyme deficiency (less than 10% of normal) and have chronic anaemia. **Class II** variants also have severe enzymedeficiency, but there is usually only intermittent haemolysis. **Class III** variant have moderate enzyme deficiency (10 to 60% of normal) with intermittent haemolysis, usually associated with infections or drugs. **Class IV** variants have no enzyme deficiency or haemolysis. **Class V** variants have increased increased enzyme activity. Class IV and V are of no clinical significance[4,17].

Altikat et al[18] studied effect of numerous drugs, chemicals and anaesthetic agents on enzymatic activity of G6PD. **Table 1** shows the list of safe and unsafe drugs from the invitro studies.

A pre-knowledge of G6PD deficiency statein a male child scheduled for tonsillectomy, adenoidectomy, adenotonsillectomy or any other surgical procedure done under general anaesthesia, should prime the surgeon and anaesthetist for the possible untoward reactions and may also influence the choice of medications and general anaesthesia administered to such patients.In order to forestall the sequelae of

the inadvertent multiple drug administrationin these susceptible individuals, deliberate dose adjustment of even the so calledsafe drugs in patients with G6PD becomes necessary.

The objective of this study is to highlight our experience and report theimmediate and late post-operative clinical conditions of G6PD deficient male patients who had tonsillectomy, adenoidectomy or adenotonsillectomy for obstructive sleep disorders.

Safeand Unsafe drugs, Chemicals and Anaesthetic agents in G6PD-deficient Population

Table 1 (Invitro study by Altikat et al[18])

Unsafe for Class i, ii and iii	Safe for Class ii and iii
Acetanilid	Acetaminophen
Dapsone	Aminopyrine
Methylene blue	Ascorbic acid
Nalidixic acid	Aspirin
Nitrofurantoin	Chloramphenicol
Niridazole	Chloroquine
Primaquine	Colchicine
Toluidine blue	Diphenhydramine
Vitamin K	Isoniazid
Sulfacetamide	L-DOPA
Sulfamethoxazole	Menadione
Sulfanilamide	Paraminobenzoic acid
Phenylhydrazine	Phenacetin
Furazolidone	Phenytoin
Trinitrotoluene	Probenecid
Thiazosulfone	Procainamide
Phenazopyridine	Pyrimethamine
Diazepam	Quinidine
Isoflurane	Quinine
Sevoflurane	Sulfamethoxypyridazine
	Streptomycin
	Sulfisoxazole
	Trimethoprim
	Tripelennamine
	Halothane
	Prilocaine
	Ketamine
	Fentanyl
	Propofol
	Benzodiazepam(except diazepam)

PATIENTS AND METHODS

STUDY DESIGN

This work is a retrospective chart reviewof male G6PD-deficient male patientswho had adenotonsillectomy at UCH,Ibadan,South-Western Nigeria from January 2008 to December 2012. Two hundred and thirty male children presented with obstructive adenotonsillar enlargement at the ENT out-patient department of UCH, Ibadan, within the period studied. Informed consent to extract datafrom medical record of patients for the study was obtained from parents and guardian of patients by telephone contacts. Demographic and clinical data of Patients were extracted from the hospital records and files. Data collated were cleaned and analyzed using SPSS version 17. Mean and standard deviation were computed for all qualitative and quantitative variables. Frequencies, percentages and cross-tabulation were used to analyze the variable data. The results were summarized and represented in figures, tables and charts. Statistical significance was set at P value = <0.005

Inclusion criteria : All G6PD-deficient male children between ages 1yr to 7yr with clinical and radiological evidence obstructive adenotonsillar enlargement with persistent complaints of snoring, noisy breathing, mouth-breathing and excessive apnoeic spells

Exclusion criteria: All female children treated for adenotonsillar enlargement and all male children treated for adenotonsillar enlargement but previously screenedto havenormal G6PD status or undetermined G6PD status. All children with adenotonsillar enlargement with co-morbidities such as allergy, sickle cell anaemia, neurological disorder, any organ failureand those above the ageof 7years.

RESULTS

Out of a total number of 236 male children that had adenotonsillectomy between January 2009 to December 2012, only 22 male G6PD-deficient patients were identifiedin the 3years retrospective review. The age-range of the study population was between 1 to 7years old.Infections and malaria was treated in all subjects before patients were scheduled for adenotonsillectomy.

All the 22 male subjects identified had G6PD-deficiency screening at the health facility of delivery sequel to development of neonatal jaundice. From the past medical history of the subjects, some have hitherto experienced episodes of drug-induced haemolytic crises or non-haemolytic reactions.

The main drugs blamed for the haemolysis were quinine, amodiaquine, sulphonamide, nalidixic acid, nitrofurantoin and vitamin K. Non-haemolytic reactions were triggered by amodiaquine, quinine, promethazine and penicillin in some of the patients.

The haemolytic crises reported prior to presentation were jaundice and altered dark coloured urine while the non-haemolytic reaction reported were atopy,itching of skin, cyanosis, blepharospasm and dystonic reaction

Historically, 15(68.2%) and 6(27.3%) of the patients in the study population subsequently developed episodes of drug- induced hemolysis and non-hemolysis prior to undergoing adenotonsillectomy by the otolaryngologists

The choice of drug used in all 22 male patients for antibiotics prophylaxis was parenteral amoviclav. Depending on anaesthetist drugs made available by the hospital pharmacy, the anaesthesiologist used different combination of anaesthetic agents and drugs intraoperatively, namely, Propofol, Halothane, Isoflurane, midazolam, fentanyl, suxamethonium, pancuronium, neostigmine, atropine, acetaminophen and pentazocine.

Propofol, pancuronium or suxamethonium, neostigmine, atropine, amoxiclav and acetaminophen were administered to all 22 G6PD deficient male patients. Seventeenpatients were given halothane, 5 patients were given isoflurane, 15 patients were given fentanyl, 7 patients were given pentazocine, 4 patients were given midazolam, and 18 subjects were given diazepam.The average estimated blood loss(EBL) at surgery for the study population was 39mls.

All 22 male G6PD-deficient were confined and observed up till 3rd post-operative day. The post-operative clinical conditions of all 22 male G6PD-deficient patients were satisfactory. None of the subjects had clinical evidence of jaundice, haemoglobinuria, cyanosis, abdominal cramps or lethargy.

None of the 22 male subjects had post-operative blood transfusion. All subjects who had mild post-op anaemia were discharged home on haematinics. Documented parental perceptions regarding the main presenting complaints were elicited at 2nd and 3rd week post-surgery.The main complaints re-appraised were snoring, mouth breathing, noisy breathing and apnoeic spells. Parents of 21 (95%)patients reported resolution of noisy breathing, parents of 20(91%) patients reported improvement in snoring and apnoeic spells. Parents of 15 (68%) patients reported improvement in mouth-breathing. The parental responses shows that despite the risk of haemolytic crises, the overall benefits of surgical treatment surpass the risk which was earlier entertained.

Statistical analysis shows that there is a strong correlation between haemolytic crises in G6PD-deficient patients and treatment with amodiaquine, quinine and sulphonamide ($P < 0.001$). No association was determined between administration of Isoflurane, fentanyl, diazepam or acetaminophen and development of haemolytic crises in the 22 male G6PD-deficient children.

The results of post-operative audit of the identified 22 G6PD-deficient male patients with obstructive adenotonsillectomy are represented in table 2,3 and figure 1 shown overleaf.

TABLE 2.SHOWING THE LIST OF VARIOUS ANAESTHETIC AGENTS AND DRUGS ADMINISTERED TO THE IDENTIFIED G6PD-DEFICIENT MALE PATIENTS(n=22)

ANAESTHETIC AGENTS AND DRUGS	FREQUENCY	PERCENTAGE
PROPOFOL	22	100
HALOTHANE	17	77.27
ISOFLURANE	5	22.72
FENTANYL	17	77.27
PENTACOZINE	7	31.82
DIAZEPAM	18	81.82
MIDAZOLAM	4	18.18
SUXAMETHONIUM	6	27.27
ACETAMINOPHEN	22	100
PANCURONIUM	16	72.73

Table 3. SHOWING PAST DRUG-INDUCED REACTION, INTRA-OPERATIVELY ADMINISTERED DRUGS AND POST-OPERATIVE CLINICAL CONDITION OF THE G6PD-DEFICIENT PATIENTS(n=22)

S/N	A	B	C	D	E	F	G	H	I	J	K
1	1	Yes	1	Nil	Amodiaquine	31 %	30ml	Propofol,halothane,diazepam,fentanyl, acetaminophen,pancuronium	29 %	Stable	Stable
2	1	Yes	1	Nil	Amodiaguine	30 %	45mls	Propofol, halothane, diazepam, fentanyl,acetaminophen,pancuronium	28 %	Stable	Stable
3	1	Yes	0	Cyanosis	Quininine	32 %	30mls	Propofol,isoflurane,diazepam,fentanyl, acetaminophen,pancuronium	30 %	Stable	Stable
4	1	Yes	1	Nil	Quinine	31 %	45mls	Propofol,isuflorane,diazepam,fentanyl,acetaminophen,suxamethonium	29 %	Stable	Stable
5	1	Yes	1	Nil	Vitamin K	33 %	30mls	Propofol,halothane,diazepam,fentanyl,acetaminophen,suxamethonium	29 %	Stable	Stable
6	1	Yes	1	Nil	Sulphonamide	30 %	45mls	Propofol,halothane,diazepam,fentanyl,acetaminophen,pancuronium.	28 %	Stable	Stable
7	2	Yes	0	Atopy	Penicillin	32 %	30mls	Propofol,halothane,midazolam,pentazocine,acetaminophen,suxamethonium	30 %	Stable	Stable
8	2	Yes	1	Nil	Quinine	32 %	45mls	Propofol,isuflorane,midazolam,fentanyl,acetaminophen,pancuronium	30 %	Stable	Stable
9	2	Yes	1	Nil	Amodiaquine	33 %	30mls	Propofol,halothane,diazepam,pentazocine,acetaminophen,pancuronium	31 %	Stable	Stable
10	2	Yes	1	Nil	Nitrofurantoin	32 %	35mls	Propofol,halothane,diazepam,pentazocine,acetaminophen,pancuronium	29 %	Stable	Stable
11	2	Yes	2	Nil	Amodiaquine	31 %	30mls	Propofol,halothane,diazepam,fentanyl,acetaminophen,suxamethonium	28 %	Stable	Stable
12	2	Yes	0	Nil	Nalidixic acid	34 %	35mls	Propofol,halothane,diazepam,fentanyl,acetaminophen,pancuronium	30 %	Stable	Stable
13	2	Yes	0	Itching	Amodiaquine	32 %	45mls	Propofol,isuflorane,diazepam,pentacozine,acetaminophen,pancuronium	29 %	Stable	Stable
14	2	Yes	0	Blepharo spasm	Promethazine	32 %	40mls	Propofol,halothane,midazolam,fentanyl,acetaminophen,pancuronium	30 %	Stable	Stable
15	2	Yes	1	Nil	Quinine	31 %	35mls	Propofol,halothane,midazolam,pentazocine,acetaminophen,suxamethonium	29 %	Stable	Stable
16	2	Yes	2	Nil	Sulphonamide	32 %	30mls	Propofol,halothane,diazepam,fentanyl,acetaminophen,pancuronium	30 %	Stable	Stable
17	3	Yes	0	Dystonia	Promethazine	32	40mls	Propofol,halothane,diazepam,fentanyl,acetaminophen,pancuronium	30 %	Stable	Stable
18	3	Yes	1	Nil	Amodiaquine	31	35mls	Propofol,halothane,diazepam,fentanyl,acetaminophen,pancuronium	29 %	Stable	Stable
19	3	Yes	1	Nil	Quinine	30	45mls	Propofol,halothane,diazepam,pentazocine,acetaminophen,suxamethonium	29 %	Stable	Stable
20	3	Yes	1	Nil	Amodiaquine	32	40mls	Propofol,halothane,diazepam,pentazocine,acetaminophen,pancuronium	30 %	Stable	Stable
21	5	Yes	0	Itching	Amodiaquine	34	50mls	Propofol,Isoflurane,diazepam,fentanyl,acetaminophen,pancuronium	31 %	Stable	Stable
22	6	Yes	1	Nil	Sulphonamide	34	45mls	Propofol,halothane,diazepam,fentanyl,acetaminophen,pancuronium	32 %	Stable	Stable

A= Ages of male G6PD-deficient subjects in years G= Estimated blood loss at surgery

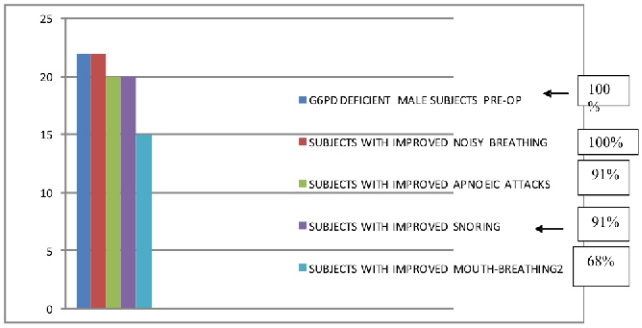
B= G6PD screening test after birthH= Anaesthetic agents and drugs

C= Frequency of haemolysis in the pastI= Post-op PCV

D= Non-haemolytic reactionsJ=Early post-op symptoms

E= Trigger agent or drugs F=Pre-op PCVK= Late post-op symptoms

Figure 1 (n=22)



POST-OPERATIVE PARENTAL PERCEPTION OF THE IDENTIFIED G6PD-DEFICIENT MALE PATIENTS FOUR WEEKSAFTER ADENOTONSILLECTOMY BY TRADITIONAL DISSECTION METHOD

Discussion

The hospital prevalence of G6PD-deficiency seen in male children attending ENT clinicUCH Ibadan for the treatment of obstructive adenotonsillar enlargement was found to be 9.3% .This finding is understandably lower compared to the prevalence in other related G6PD studies done in Nigeria.

The low prevalence may be due to exclusion of a large population of male children who were never screened for G6PD-deficiency at any of the health facility in the past. Egesie et al[19] in Jos, North Central Nigeria, reported a prevalence of 20% among healthy males residing in Jos and quoted a prevalence of 20-26% in Western, Nigeria. Similarly, the prevalence of G6PD-deficiency among Sicklecell anemia patients attending haematology clinic at JUTH were found to be 18.5%[20].

From the past medical history of the subjects in the study population, it can be deduced that majority of the G6PD-deficient males studied belong to WHO Class III. From literature, infection is noted to be the most common factor inciting hemolysis in G6PD-deficient patients. Patients planned for adenotonsillectomy may be harbouring sub-clinical tonsillar, adenoidal or respiratory tract infections which may not be clinically obvious. Furthermore, the areas to be operated in the oropharynx and nasopharynx are potentially contaminated cavities. Therefore, prophylactic antibiotic was necessarily given intra-operatively to prevent infections that may flare up after surgery. Findings from the study show that anaesthetic agents and drugs mentioned in literature to be precipitants of haemolysis in G6PD-deficient cells did not show a positive association with development of haemolysis. The anaesthetic agents used during the surgeries performed on the study population include Isoflurane, acetaminophen, midazolam and diazepam. This finding is sharply in contrast to the works of Altikat and co-workers[18].They reportedin literature that from their invitro studies of the effect of anaesthetic agents on G6PD-deficient cells,isoflurane, sevoflurane, diazepam and midazolam had an inhibitory effect on G6PD activity and subsequently resulting in haemolytic crises. On the contrary, according to a Lancet publication, the association between acetaminophen and haemolysis' is doubtful[4].

From the review of clinical signs and symptoms in the male G6PD-deficient study population at UCH, ENT department, haemolysis was not observed in the immediate post-operative period. This finding is not consistent with report in literature[4] which alluded that following the administration of general anaesthesia(Isoflurane, midazolam, diazepam or sevoflurane) in G6PD-deficient patients, clinical signs and symptoms of haemolysis typically arises 24 to 72hour of drug dosing and anaemia worsens until about the 7th day.

The positive associations seen between haemolytic crises and drug treatment from the past drug history of the study population strongly agrees with the works of Beutler[7] and Altikat[18]. It was therefore advisedthat medications such as dapsone, flutamide, mafenide cream methylene blue, nalidixic acid, nitrofurantoin, phenazopyridine, primaquine, sulfacetamile and vitamin K should be avoided by persons with G6PD-deficiency[21]. Thetrigger drugs in our study were amodiaquine, quinine, sulfadoxine-pyrimethaminecombination, nitrofurantoin, vitamin K and nalidixic acid.

Good service delivery requires continued quality improvement and feedback from clients to know their perception and expectation. Satisfaction occurs when services meet or exceed the client's expectation or desires. Evaluation of quality of health care, although complex and challenging, cannot be ignored nowadays. This trend has informed the establishment of total quality care unit in government-owned tertiary hospitals in Nigeria. In other to elicit the parental perception in our study, documented parental complaint of residual or persistent symptoms during the post-operative follow-up in the 2nd and 4th week was analyzed.

The clinical progress report of the patients provided a template to evaluate the efficacy of adenotonsillectomy in the clinically susceptible

patients against the backdrop of potential complication of hemolysis. Statistically, the data shows that all the 22(100%) parents of the G6PD-deficient male patients were appreciative of the disappearance of noisy breathing, 20(91%) of the parents expressed satisfaction over the objective improvement of snoring and frequent apnoeic attacks and 15(68%) of the parents observed reversal of mouth-breathing. It can be speculated that this disparity may be due to the chronicity of nasal obstruction in 7 of the patients; hence, a longer period of follow-up may be necessary to observe the desired outcome. Generally, improvement in patients' symptoms was observed in 68-100% in our study population. This finding is in close conformity with work of Ologe et al[22] who reported symptoms disappearance of 75.9-96.6% in their study population. On the contrary, Maw[23]who reported a lower reduction in symptoms. In the study, 59% improvement of symptoms was observed 6wk after adenotonsillectomy and 62% improvement of symptoms was subsequently observed one year after surgery.

CONCLUSION

We acknowledge the limitations of small sample size in the study population and lack of assay of serum bilirubin level to determine microscopic haemolytic crises, however, the findings of the study shows that provided infection is treated prior to surgery, parents and surgeons should not entertain undue fear of drug-induced hemolysis in G6PD-deficient male children undergoing surgery thereby leading to withholding of important surgical intervention. Self-reportage of hemolysis and non-haemolytic reaction from drugs such as amodiaquine, quinine and sulphonamide are worrisome. Retrospectively, none of the subjects had haemolytic crises arising from effect of anaesthetic agents and 68-100% of the presenting symptoms were adduced to have resolved by theparental accounts of the G6PD-deficient male patients.

We declare no conflict of interest in our study on post-operative audit of male G6PD-deficient patients with obstructive adenotonsillar enlargement.

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