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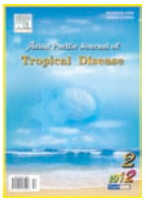

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Profile of seizures in adult falciparum malaria and the clinical efficacy of phenytoin sodium for control of seizures

Manoj Ku Mohapatra[1*], Laxmi Kanta Dash[2], Nihar Ranjan Mishra[2], Ritesh Ku Agrawala[2]

[1]*Department of Medicine, VSS Medical College, Burla, Odisha, India*
[2]*VSS Medical College, Burla, Odisha, India*

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ABSTRACT

Objective: To study the profile of convulsion in adult severe falciparum malaria and efficacy of phenytoin sodium for its control. **Methods:** It comprised of two sub studies. Study-1 evaluated the pattern and risk factors of seizure in severe malaria and Study-2 investigated the efficacy of phenytoin sodium to control seizure in an open label trial. Patients of severe malaria were diagnosed as per WHO guideline. Clinical type and duration of convulsion were determined. Biochemical and haematological investigations including EEG and CT scan of brain were performed in all cases. All patients were treated with injection artesunate along with other supportive measures and patients with convulsions were treated with injection phenytoin sodium. **Results:** Out of 408 patients of severe malaria 118 (28.9%) patients had seizure. Generalized tonic clonic seizure, partial seizure with secondary generalization, and status epilepticus was present in 89(75.4%), 25(21.2%), and 4(3.4%) cases respectively. CT scan was abnormal in 16 (13.6%) cases. EEG was abnormal in 108 (91.5%) cases showing generalized seizure activity. Patients with convulsion (n=118) were treated with phenytoin sodium injection and convulsion was controlled within 12 hours [mean (6.2±2.1) hours] of treatment in 107 (90.6%) patients. Recurrence of seizure occurred in 2 (1.7%) patients and 11 (9.3%) patients did not respond. The mortality and sequelae were more among patients with than without convulsion. **Conclusions:** Seizure is common in adult falciparum malaria and phenytoin is an effective drug for seizure control.

1. Introduction

Malaria is no more a simple febrile illness characterized by fever with chill, rigor and related symptoms. If not diagnosed early and treated promptly it can progress to severe malaria that include cerebral malaria, renal failure, jaundice, acidosis, acute respiratory distress syndrome, anaemia and coagulopathy[1,2]. Further it may lead to a multi organ dysfunction (MODS) like state and death[2]. Out of all species of plasmodia that cause human malaria, *Plasmodium falciparum* (*P. falciparum*) has the potentiality to progress to severe malaria causing death and it has been estimated that 1-3 million deaths per year occur due to severe malaria worldwide[3].

Cerebral malaria is the most commonly encountered complication of falciparum malaria. Acute seizures are common in cerebral malaria, particularly in young children and are present in about 60% of the cases associated with prolonged coma and increased risk of neurologic sequelae and death[4]. Seizure is also an important clinical presentation of adult falciparum malaria but few investigations addressed about it, and that was in context of a broader description of clinical profile of severe malaria[5,6].

Severe falciparum malaria is a complex syndrome whose mechanism is thought to be related to sequestration of parasitized red blood cells (PRBC) in the cerebral microcirculation. It leads to profound impairment in cerebral microcirculation causing hypoxia and organ dysfunction[7]. It has been found both experimentally and clinically that prolonged seizure irrespective of cause both in children and adults can cause neuronal damage such as mesial necrosis in the hippocampal area, cortical infarction and atrophy[8]. Superimposition of seizure over an existing

*Corresponding author: Dr. MK Mohapatra, Professor and Head, Department of Medicine, V.S.S. Medical College, Qr. No.C/1 Doctors Colony, Burla, Sambalpur, Odisha, 768017.
Fax: 0663 2430768
E-mail: mohapatra.manoj@rediffmail.com

altered tissue perfusion state like cerebral malaria may further aggravate hypoxia and cause hypoglycemia and increased intra cranial pressure which can further increase neuronal damage[8]. Therefore rapid termination of seizure and prevention of prolonged and repetitive convulsion should be one of the goals of treatment of malaria. But the management of seizures still remains as an area of uncertainty due to lack of trials on use of different anti epileptic drugs in malaria in general and adult malaria in particular. Most of the trials have been done in children and those drugs have been used in adults without any trials[9-11].

Therefore, we have planned this prospective study to find out profile of seizures in adult severe malaria and the effect of phenytoin sodium on seizures in an open label trial.

2. Material and methods

This study was carried out in Department of Medicine, V.S.S. Medical College Hospital, Burla, Sambalpur, Odisha from October 2009 to September 2011. It comprised two parallel sub studies, *i.e.*, one evaluating the pattern, possible mechanism, and risk factors of seizure in adult malaria (Study-1) and the other investigating the efficacy of phenytoin sodium as anticonvulsant to control seizure (Study-2).

2.1. Study-1

Study-1 is a prospective observational study in which all adult patients (18-65 years) of severe falciparum malaria who tested positive for asexual stage of parasite were admitted to the Department of Medicine and enrolled in the study. The patients with seizures underwent a complete physical examination, and the details were noted in a specifically designed proforma.

The diagnosis of falciparum malaria was made with detection of asexual form of the parasite in the Giemsa stained peripheral blood smears. Parasite concentration was determined on the basis of the number of asexual parasites including ring forms, trophozoites, and schizonts per 200 leukocytes. The number of parasites per 200 leukocytes was multiplied by total leukocyte count to give a quantitative count per microliter. Smear was taken 12 hourly to know the parasite status with treatment. Severe malaria was defined according to the WHO criteria[12]. Glasgow coma scale (GCS) score determined the grades of coma. The biochemical investigations such as blood glucose, blood urea, serum creatinine, serum sodium, serum albumin, serum bilirubin, aspartrate amino transferase (AST), alanine amino transferase (ALT) and complete blood count (CBC) including blood grouping were done in all cases. We also conducted a cerebrospinal fluid analysis, abdominal ultrasound, chest X-ray, electrocardiogram, and serological markers for hepatitis to exclude the diseases mentioned in exclusion criteria.

All patients were treated with artesunate injection (2.4 mg/kg) at 0 h, 12 h, 24 h once daily for 7 days or continued until they were able to tolerate drugs orally according to WHO guidelines[13]. Then sulfadoxine-pyrimethamine was given orally. Supportive treatment was given as per requirement. Hypoglycaemia was treated with an intravenous injection of 25% dextrose followed by a continuous infusion of 10% dextrose. Oliguric acute renal failure *i.e.*, urine output < 400 mL/day associated with rising serum creatinine despite rehydration and a trial of diuretics was treated with haemodialysis. Patients who developed adult respiratory distress syndrome were intubated and ventilated with positive end expiratory pressure if indicated.

Patients with co-morbid conditions like diabetes mellitus, chronic renal failure, hypertension, coronary artery disease, valvular heart disease, chronic liver disease, alcoholic liver disease, associated infections (*e.g.* pneumonia, urinary tract infection, viral hepatitis, meningitis), and who lost follow up were excluded from the study.

The details of the convulsion *e.g.* type and duration of convulsion was recorded. The clinical types of convulsion were defined as per the definition of international union against epilepsy14. Seizure has been defined as any clinical event caused by an abnormal electrical discharge in the brain and the motor event is known as convulsion. For the present study motor seizure (convulsion) has been described as seizure. Status epilepticus (SE) has been defined as a seizure or series of seizures lasting 30 minutes without the patient regaining awareness between attacks. Mostly this refers to recurrent tonic-clonic seizures. Prolonged seizure is the seizure that lasts for more than 5 minutes but less than 30 minutes[15]. If seizure occurred within 48 hours of onset of fever we considered it as early onset fever and after 48 hours of fever as late onset seizure.

The study protocol was approved by the ethics committee and written informed consent was obtained from all subjects before the study commenced.

2.2. Study-2

Study-2 is an open label and non-randomized trial. In this part of study we included patients of malaria who had seizure at the time of presentation or who developed it during the hospital stay after initiation of treatment and excluded the patients who received diazepam, paraldehyde, phenobarbitone or any other anticonvulsant before hospitalization.

In addition to the treatment described above in Study-1 phenytoin sodium was administered for control of convulsion. Phenytoin was diluted with normal saline to a final concentration of 8 mg/mL and a loading dose of 15 mg/kg was infused over 20 minutes and then a maintenance dose of 2.5 mg/kg infused over of 5 minutes was administered 12 hourly for 48 hours. Oxygen saturation, blood glucose level during convulsion and 5 minute postictal evaluation was also recorded. We have used intravenous lorazepam as the additional drug when there was failure of phenytoin sodium. The recommended dose of lorazepam was 0.1 mg/kg administered at a rate of 2 mg/minute[16]. The dose was repeated after 10-15 minute if seizure did not stop.

The following outcome definitions have been followed in this study. a) A single seizure was considered to be terminated if it stopped within 30 minutes of drug administration. It also held good for prolonged seizure and SE with the duration of seizure 30 minutes or more. b) Convulsion was considered to be controlled when there were no convulsions within 12 hours of termination of seizure. c) SE with repetitive episodes of seizures of short

duration has been considered to be controlled adequately when there were no convulsions within 12 hours without additional anticonvulsant. d) Seizure recurrence was defined when a patient developed seizure within 72 hours of control of seizure. e) Drug is considered not effective when an additional anticonvulsant is used for termination or control of seizure and there is seizure recurrence. Any adverse drug reaction to phenytoin sodium was also recorded. All patients in this study had electrocardiographic monitoring from the initiation of treatment to 8 hours thereafter. The study protocol was approved by the ethics committee and written informed consent was obtained from each subject prior to starting the study. The outcomes measured are control of convulsion and recurrence of convulsion during follow up. All the patients were followed up for 6 months.

2.3. Statistic analysis

Data were analyzed using SPSS-11 and expressed as mean standard deviation. Univariate Cox proportional hazard model is used to find out risk factors associated with seizures. Comparison among groups was performed using student's *t* test and *Chi* square test.

3. Results

3.1. Study-1

During the study period 408 patients of severe malaria were admitted to the hospital. Of them 110 (26.9%) patients had seizure at the time of admission and 8 (1.9%) patients developed convulsion during the treatment and were included in the analysis. Thus there were 118 (28.9%) patients with seizures. Of them there were 77 (65.2%) males and 41 (34.7%) females with a male: female ratio of 1.8:1. Generalized tonic clonic seizure (GTCS), partial seizure with secondary generalization, and status epilepticus was present in 89 (75.4%), 25 (21.2%), and 4 (3.4%) cases respectively. Early onset seizure [(21.1±12.8) hours] was found in 11 (9.3%) cases whereas late onset seizure [(79.6±17.5) hours] was found in 107 (90.7%) cases. Short duration seizure, prolonged seizure, and SE were found in 85 (72.1%), 29 (24.6%), and 4 (3.4%) cases respectively (Table 1). The mean duration of short seizure was (2.2±1.2) minutes and of prolonged seizure is (5.8±1.1) minute. The parasitic count was (8 756.3±256.3) per microliter in the seizure group which was higher than the patients without seizure (4 300.7±180.5) (P<0.001).

There were 3 independent risk factors for a patient of developing seizure in falciparum malaria. They were 1) High parasite count >5 000/μL (OR=1.8, 95% CI=1.1-2.8, P=0.01); 2) presenting with multi organ failure (OR=1.9, 95% CI=1.2-3.1, P=0.002); 3) hyponatremia (OR=4.4, 95% CI=1.4-14.3, P=0.002). The death and sequelae were higher among patients with seizure compared to patients without seizures (P<0.01).

CT scan was normal in 102 (86.4%) cases and the rest 16 (13.6%) showed abnormality. The abnormalities in CT scan were diffuse cerebral oedema in 12 (10.2%), infarction in 2 (1.7%), and intracerebral hemorrhage and intracranial space occupying lesion (ICSOL) in 1 (0.8%) case each. Secondary cause of seizure was found in 4 (3.4%) cases that included 3 cases of stroke and one case of ICSOL. Electroencephalography (EEG) was abnormal in 108 (91.5%) cases showing generalized seizure activity with abnormal awake record. The abnormality in EEG persisted in 15 (12.7%) cases for more than 6 months.

Table 1
Clinical progress of seizures.

Features	Number (Percentage)
Seizures on admission	110 (26.9)
Seizures after admission	8 (1.9)
Short duration of seizure	85 (72.1)
Prolonged seizure	29 (24.6)
Status epilepticus	4 (3.4)
Proportion of short seizure to prolonged seizure including SE	85:33 (2.6:1)

Table 2
Types of severe malaria among patients with seizure.

Type	Number (percentage)
Cerebral + jaundice + Renal failure	40 (33.9)
Cerebral + Anaemia + Renal failure	28 (23.9)
Cerebral + Anaemia + Resp. distress	5 (4.2)
Cerebral + Anaemia + Resp. distress+Renal failure	5 (4.2)
Cerebral + Jaundice	18 (15.3)
Cerebral + Severe anaemia	7 (5.9)
Cerebral	10 (8.5)
Jaundice + Renal failure	5 (4.2)

Table 3
Base line characteristics of the study population.

Characteristics	Malaria with seizure (n=118)	Malaria without seizure (n=290)
Male/Female	77/41	201/89
Age (Median/Years)	28	30
GCS	6.5±2.2	8.9±5.2*
Hb (gm/dL)	6.4±2.2	7.8±3.5
TLC (10^9/L)	9.7±2.4	8.5±1.2
Platelet (10^9/L)	120.8±80.5	180.7±50.9
Blood glucose (gm/dL)	85.4±22.5	90.5±12.5
Serum sodium (mEq/L)	114.8±8.5	128.6±14.5**
Serum potassium (mEq/L)	3.1±1.1	4.1±1.2
Serum bilirubin (mg/dL)	11.9±2.8	4.1±2.7**
SGOT (IU/L)	61.8±12.2	45.8±10.2**
SGPT (IU/L)	63.8±12.8	55.8±9.8**
Alk. Phosphatase (IU/L)	278.9±28.2	125.9±19.2**
Blood urea (mg/dL)	86.4±24.9	25.2±12.8***
Serum creatinine (mg/dL)	6.2±1.4	1.8±0.3***
Mortality	25 (21.2%)	53 (18.3%)**
Sequelae	11 (9.3%)	12 (4.1%)**

*P<0.05, **P<0.01 and ***P<0.001 compared with mlaria with seizure using *t* test.

Apart from altered sensorium and convulsion which present in all cases fever was present in 93.2% (n=110) of patients. Other common signs and symptoms included anaemia (n=98, 83.1%), generalized weakness (n=80, 67.8%), vomiting (n=56, 47.5%), decreased urination (n=70, 59.3%), and jaundice (n=60, 50.8%). Breathlessness (n=10, 8.5%), bleeding (n=3, 2.5%), and hypoglycaemia (n=2, 1.7%) were less common. Simultaneous involvements of multiple organs were common in the study. Majority of patients (33.9%) had constellation of cerebral malaria, jaundice and renal failure

(3 organ dysfunction) (Table 2). The base line characteristics were presented in Table 3.

3.2. Study-2

118 patients of malaria with convulsion were treated with injection phenytoin sodium along with antimalarial drug. Generalized tonic clonic seizure (GTCS), partial seizure with secondary generalization, and SE was present in 89 (75.4%), 25 (21.2%), and 4 (3.4%) cases respectively. Out of 4 cases with SE, 1 patient had prolonged seizure that lasted for 30 minutes or more and rest 3 had frequent short duration of seizure. Mean time interval of seizure onset to administration of phenytoin was (6.3±4.2) hours.

Termination and control of seizure was observed in 107 (90.6%) patients of which 74 (69.2%), 23 (21.5%), and 10 (9.4%) patients became seizure free within 4, 8, and 12 hours respectively. The mean time for seizure control was (6.2±2.1) hours. Recurrence of seizure occurred in 2 (1.7%) patients and the duration was only for 1 minute. Both the patients were managed with a single additional dose of lorazepam injection. Termination of seizure did not occur in 11 (9.3%) patients. All these phenytoin failure cases belonged either to prolonged seizure (9 patients) or to SE (2 patients). If we combined patients of prolonged seizure and SE then 37.9% (11 out of 29) patients did not respond to phenytoin. Hence, lorazepam injection had been added. With addition of *i.v.* lorazepam seizure was contolled within 30 minutes and there was no recurrence. After control of seizure with lorazepam, phenytoin had been administered at maintenance dose. With administration of phenytoin seizure was controlled within 18 hours and there was no recurrence. The mean interval of onset of seizure to initiation of phenytoin administration was (5.6±4.1) hours. No patient had developed any adverse drug reaction. The mean concentration of phenytoin sodium after 6 hours of administration was 10.4 μg/mL (normal range: 10.0-18.0 μg/mL).

The mortality among the patients with seizures was 21.2% (25 of 118) which is higher ($P<0.01$) compared to 18.3% (53/290) mortality without seizures with an overall mortality of 19.1% (78 of 408). Among the survivors, 11 (9.3%) patient had neurological sequelae. The sequelae were psychosis, hemiplegia, extra pyramidal rigididty, and cerebellar ataxia in 5 (45.4%), 3 (27.3%), 2 (18.2%), and 1 (9.1%) cases respectively. Patients without seizure also had neurological sequelae but it is less than the former (12/290, 4.1%, $P<0.01$) and the manifestations were also different. Hemiplegia was not found in the later group. The sequelae were psychosis (7/12, 58.3%, cerebellar ataxia (3/12, 25.0%), and extra pyramidal rigidity (2/12, 16.7%). The overall sequelae was 5.6% (23/408). On follow up persistence of abnormal EEG was present in 15 (12.7%) cases and they require maintenance phenytoin sodium.

4. Discussion

Unlike childhood malaria, seizures in adult malaria are a less described entity. The present research revealed that seizure in adult malaria is common and phenytoin sodium is an effective anticonvulsant to control the seizure in such patients.

Out of 4 species of plasmodia that commonly cause human malaria, *P. falciparum* is notorious for development of various complications that lead to severe malaria. Cerebral malaria, which is a diffuse acute vasculopathy and characterized by coma is the most common form of severe malaria. After coma, seizure is the next common central nervous system manifestation of falciparum malaria. The present study showed that 28.9% of adult falciparum had convulsion during the course of the disease and is in accordance with other two studies that showed 17.1% and 21.3% adult malaria patients had seizures[5,6]. It showed that SE is less common in adult malaria and seizure of short duration is more frequent.

Contrary to adult patients, convulsion is present in about 30% of African children admitted to the hospital with cerebral malaria and about 60% develop convulsion during hospitalisation and common presentation is SE[4]. Higher incidence of seizure was also found in Indian children with severe malaria[17-19]. Another important observation of the study is that only 1.8% adult patients of severe malaria developed convulsion after hospitalisation and the convulsion is of short duration. The increased incidence of SE may be due to seizure vulnerability of the developing brain[18]. Experimental and clinical data showed that alterations in synapses, ion channels and peptide transmitters take place in developing brain. These changes increase the excitability of the brain to various stimuli (*e.g.* metabolic, electrical and/or chemical) and also fail to suppress the adverse convulsive effects of such stimuli increasing the seizure susceptibility[20]. In adult brain such types of physiological alterations do not occur. Therefore, probably seizure is less common in adult malaria than paediatric population. Due to less frequency of seizures after hospitalisation and initiation of antimalarial drug, prophylactic aniconvulsants should not be given routinely to all patients of severe malaria.

According to onset, we encountered 2 distinct types of acute seizures in adult malaria *i.e.* early onset and late onset seizure. Early onset seizure occurred within 48 hours of onset of fever. Secondary cause was found in 4 (3.4%) cases which implied that malaria may precipitate the convulsion. Seizure has been described as a late sequelae of malaria. Recently epidemiological studies showed that cerebral malaria is a cause of epilepsy in children[21]. However in adults the data is scanty. In our study with follow up we could detect persistence of abnormal EEG in 12.7% cases and they developed further convulsions requiring prolonged anti epileptic drugs. Further epidemiological study is necessary to show the causal relation of malaria with epilepsy in adults.

The mechanism of acute seizure in cerebral malaria seems to be multifactorial. The pathogenesis of cerebral malaria is related to sequestration of PRBC in the cerebral microcirculation. The sequestration along with aggregation of non-parasitized RBCs to the PRBC forming rosettes leads to profound impairment in cerebral microcirculation causing hypoxia[12]. Pathologic examination revealed vasculopathy with haemorrhage and formation of granuloma of Durck by astroglial reaction[12]. These lesions may give rise to seizures in malaria. Further inflammatory mediators like TNF and other interleukins are found to contribute for the genesis of seizures. These inflammatory mediators also play important roles in the pathogenesis of severe malaria. Hence, its

contribution for genesis of convulsion cannot be ruled out. Additionally, metabolic and electrolyte abnormalities during the course of severe malaria also induce seizure. All these lead to micro vascular congestion, break down of blood brain barrier, raised intra cranial pressure, and micro as well as large vessel occlusion causing seizure. Apart from these some specific effect of *P. falciparum* to the brain may also cause seizures.

The present study showed that phenytoin sodium is effective in controlling seizure and also preventing subsequent convulsion. However, in about 1/3 rd cases with prolonged seizure including SE, second drug has been added for termination of seizure. After termination, with phenytoin there was no recurrence of convulsion. Therefore, phenytoin is not very effective in terminating pronged seizure including SE. There is no available study to compare our results except one study on childhood malaria[11]. In that study in spite of adequate blood level, phenytoin failed to control status epilepticus in 53% cases. The poor response has been explained by the prolonged duration of seizure prior to the administrations of drugs. It has been observed that prolonged convulsion (> 10 min) neither stops spontaneously nor respond to anticonvulsants[7]. Further in that study out of 38 patients 27 patients had received fosphenytoin. Fosphenytoin is a pro drug that has been hydrolyzed to active phenytoin by the enzyme phosphatases in the blood and vascular tissues[11]. The activity of phosphatases gets reduced in hypoxic states and in severe malaria there occurs tissue hypoxia that may reduce the activity of phosphatases. Good response of phenytoin sodium in our series may be due to increased number of patients with short seizure and not using fosphenytoin.

The present study has some limitations. First, continuous phenytoin assay is not possible. Therefore, the pharmaco-dynamic study could not be done. Secondly, as per the recommendation of the Ethical Committee we have to administer phenytoin sodium to all the patients with convulsion. Therefore, we could not know the percentage of cases that may have spontaneous stoppage of seizure. In spite of these limitations, it is largest series of cases with seizure in adult malaria which showed that seizure is common in adult malaria and phenyton is a drug of choice for seizure in adult malaria.

Conflict of interest statement

We declare that we have no conflict of interest.

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