ANESTHETIC ASPECT OF MALARIA DISEASE: A BRIEF REVIEW

Tong SaaChai, Jun Lin*

Abstract

Background: Malaria has caused an estimated 190-311 million cases in year 2008 alone and around 1500 patients are diagnosed with the disease annually in the United States. Out of these numbers, few of them have presented for surgery. Malaria disease is a multi-organ systemic disease that may affect significantly patient's outcome after surgery. It is therefore prudent for the anesthesiologists, from both the endemic and non-endemic area, to understand the implication of the disease during the preoperative, intraoperative and postoperative course.

Methods: Google scholar, Medline and Cochrane data base search are performed using keywords malaria, anesthesia, quinine, dapsone, clindamycin, mefloquine, surgery, wound healing, cardiopulmonary bypass and obstetric. Bibliographies are systemically analyzed and grouped base on clinical presentation and potential anesthetic implication.

Key words: Malaria, Anesthesia, quinine, dapsone, clindamycin, mefloquine, surgery, cardiopulmonary bypass, wound healing, obstetric.

Introduction

Malaria is a multi-organ systemic disease caused by the genus *plasmodium.* According to the World Health Organization World Malaria Report in 2009, malaria has caused an estimated 190-311 million clinical episodes in year 2008 alone. Out of these numbers, an estimated 708,000 to 1,003,000 patients have died[1]. Malaria is a disease transmitted by mosquito species *Anopheles*. Four malarial species are closely linked to the disease: plasmodium falciparum, plasmodium vivax, plasmodium malariae and plasmodium ovale. P. falciparum infection is the most common disease out of all. Geographically, malaria disease is most prevalent in countries in the sub-Saharan region. In the U.S only approximately 1500 cases of malaria were reported yearly[1] From year 1963 to 2001, 123 deaths involving U.S travelers have been reported to the Center for Disease Control (CDC)[2].

Patients with malaria may present for surgery for both traumaticor non-traumatic reasons. To date, few literature exists to describe the anesthetic implication of the disease. In the endemic area, the implication of the disease is significant as anesthesiologists are constantly involved in the management of patients from both the operative and the postoperative course.

One of the most common surgical conditions that bring patient with malarial disease for surgery is *tropical splenomegaly*[3]. Splenic rupture is encountered occasionally with

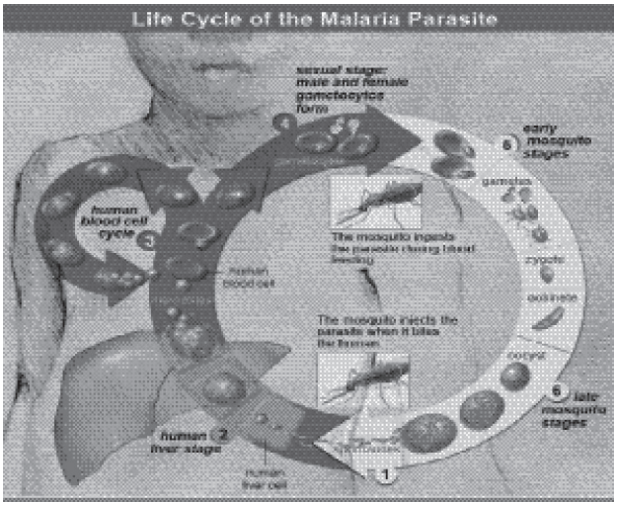
* Department of Anesthesiology, State University of New York-Downstate Medical Center, 450 Clarkson Avenue Box 6, Brooklyn, NY 11203; Correspondence: Dr. Tong Saa Chai @ tongsaa@gmail.com, or Dr. Jun Lin @ Jun.Lin@downstate.edu

trauma and may present as an emergent case[4]. Other less common surgical conditions include creation of arterial- venous fistula for renal failure, liver transplant, renal transplant and cardiac transplant. Occasionally, pregnant women with malarial disease may present for an emergent caesarean section or epidural[5].

Life Cycle

Fig. 1

Life cycle of malaria parasite (Courtesy: National Institute Of Allergy And Infectious Disease)



The knowledge of malarial disease may not be complete without a full understanding of the life cycle. In general, there are two major hosts for malaria parasites: (1.) primary host, which only involves the female species of the *Anopheles* mosquitoe and (2.) secondary host, which involves either human being or other vertebrae. The typical life cycle of malaria parasite in human body begins with the deposition of *sporozoite* into bloodstream by the *Anopheles* mosquitoe. The sporozoite replicated within the liver cells to form a new stage, *schizonts* which contains replica of *merozoites*. This is followed by the death of hepatocytes, with rupture of hepatocyte cell membrane and release of *meroziotes* into the bloodstream. This commences a cascade of invasion of red blood cells by the *meroziotes*, where the species multiples asexually within the red blood cells, which are followed by hemolysis of the red cell secondary to heavy parasitic load. The newly released merozoites then infect fresh red cell, causing a cascade of red cell infections. *Merozoites* may travel to the cerebral and splenic circulation, causing splenomegaly and cerebral malaria.

Clinical Manifestation

The severity of malarial disease is classified loosely based on the parasite load and the clinical presentation into two broad categories: *uncomplicated malaria* and *complicated malaria*. Uncomplicated malaria involves spectrum of illness which is less severe in origin. It may include non-specific symptom such as nausea, vomiting, headache, cough, myalgia, diarrhea and athralgias. Complicated malaria involves high parasite load with more severe clinical presentations, with involvement of any of the following: metabolic acidosis, acute respiratory distress syndrome, hepatic failure, liver failure and severe anemia.

Anesthetic Concern

Central Nervous System

With uncomplicated malaria, neurological symptoms may be limited to headache, nausea and vomiting. However, complicated malaria may cause raised intracranial pressure and change in mental status. Airway protection is therefore mandatory for patient who losses airway control. Increased intracranial pressure is largely the result of cerebral edema caused by vasocapillary obstruction with parasitized red cells[6]. The constellation of finding involving increased intracranial pressure, cerebral edema and change in mental status is known as '*cerebral malaria'*.

Volatile agents should be used prudently to inn the patient with increased intracranial pressure, , since it may worsen cerebral edema by increase in cerebral blood flow caused by volatile anesthetics. However, no study involving patients with cerebral malaria receiving volatile anesthetics has been performed. Thiopental and propofol have theoretical advantage over volatile anesthetics by decreasing intracranial pressure in patients with cerebral malaria, which is supported by their therapeutic effects in patient with vasogenic edema secondary to trauma. However, lack of systemic trial again precludes the conclusion that the agent has any significant effect in this patient category.

Diazepam has been demonstrated to be effective as antiepileptic in children with cerebral malaria[7]. Benzodiazepine has high therapeutic index and can be a safe anxiolytic in patients with malarial disease,

though proper monitoring would be prudent. No study was performed to date involving lorazepam or shorter acting benzodiazepine midazolam.

Hematological System

Hematological aspect of malaria includes splenomegaly, anemia and thrombocytopenia. A decrease in leukocyte count may occasionally be observed.

Splenomegaly in patients with chronic malaria is caused by the sequestration of hemolyzed red cells within sinusoids. Clinically, splenomegaly may lead to consumptive thrombocytopenia. *Tropical splenomegaly syndrome* is a poorly understood condition where patient presents with an elevated malarial antigen, hypersplenism but with very minimal parasite load[3].

Severe anemia in patients with malaria disease can be either caused by hemolysis or red cell dysplasia. Expert opinion for transfusion in malarial disease is such that adults with hematocrit level below 20% of normal and children with hematocrit below 15% should be transfused[7]. For patients with life threatening anemia, exchange transfusion should be considered. Splenectomy is reserved after medical therapy has failed[3]. The concern of splenectomy is its high surgical mortality and also risk of *pneumococcal*, *Haemophilus influenza* and *Neisseria meningiditis* infection.

Transfusion transmitted malaria has rarely been an issue in the United States with malarial ELISA detection technique. So far, only 14 cases of transfusion transmitted malaria are reported from year 1990 to 1999[9].

Cardiopulmonary bypass in patients with malaria for open heart surgery may worsen the underlying hemolysis[10]. This possibility has brought suggestion that open heart surgery in this patient population should be done with off-pump technique. Chemo-prophylaxis with antimalarial agents is virtually indicated in every patient undergoing surgery to decrease malarial load.

Cardiovascular System

Congestive heart failure in patients with malarial disease is multifactorial. Severe anemia may cause high output cardiac failure. Quinine toxicity related to malarial treatment can lead to heart failure also. Anesthetic monitoring will therefore include close monitoring with arterial line and central venous catheter or Swan-ganz catheter when indicated.

Splenomegaly may cause profound hemodynamic changes. This observation is most prominent with aorto-caval compression. Supine positioning may exacerbates hemodynamic instability secondary to aortocaval compression.

In patients with severe malaria, pulmonary artery catheter may show two possible changes: elevated pulmonary artery wedge pressure with severe heart failure and a normal pulmonary wedge pressure with no cardiac involvement[11].

Pulmonary System

In general, there are three lung conditions related to malaria that may pose an issue to the anesthesiologist, including noncardiogenic pulmonary edema, fluid overload and pneumonia[11].

The mechanism behind noncardiogenic pulmonary edema in patients with malaria is largely unknown and is believed to be caused by the breakdown of alveolar-capillary interface induced by malaria. Fluid overload is commonly observed in this population because of prevalence of renal failure and fluid shift caused by hormonal imbalances[11].

Anesthetic consideration in this group of patient therefore involves one of several aspects. In patients with impending pulmonary edema, judicious fluid management to keep the patient 'dry' may be indicated. The goal of ventilation is to maximize tissue oxygenation and this can be done accomplished by maintaining hemoglobin level above 12mg/dL, and or optimal ventilation setting with PEEP or CPAP.

Renal System

Acute renal failure is the most common renal manifestation and around 50-80% of patients require hemodialysis. Creatinine clearance level should therefore be determined before surgery. The etiology of renal failure may involve in mechanical obstruction by erythrocytes in the glomerular capillaries, or immune mediated[12]. As mentioned above, judicious fluid management is indicated as fluid overload in

patients with renal failure may implicate pulmonary edema. Dosing of non-depolarizing muscle relaxants, benzodiazepine and narcotics should be done base on underlying renal function.

Electrolyte abnormalities are commonly found with malarial acute renal failure. The most common abnormalities observed are hyperkalemia and hyponatremia[13]. Dilutional hyponatremia is the most common etiology for hyponatremia and is caused by fluid overload, although excess serum ADH levels are involved in the pathophysiology. In term of hyperkalemia, it is usually accompanied by metabolic acidosis and hemolysis and is seen in patients with *complicated malaria*. Profound hyperkalemia caused by hemolysis can be fatal.

Endocrine System

Hypoglycemia is commonly observed in severe malaria. The incidence of hypoglycemia is increased with the severity of malarial disease. The etiology is multifactorial and probably related to starvation, utilization of blood glucose by the malarial parasite and quinine therapy. Intraoperative serum glucose monitoring is therefore mandatory with clinical suspicion.

Dermatological System

Dermatological manifestation caused by malarial disease is rarely encountered. It may include symptoms like urticarial, purpura or angioedema[14].

Post-injury malaria is associated with a higher incidence of wound infection in trauma patients[15]. The cause for this temporal relationship remains unknown. It may be related to post-trauma immune-suppression or directly related to malaria parasites. Whether the same relationship exists in other surgical populations is not known as no investigation has been performed.

Malaria Treatment Guideline

Most patients who presented for surgery are on one or more chemo-prophylactic agent for malaria disease. Traditionally, the antibiotic treatment for malaria disease are broadly divided into two groups: (1) Chloroquine susceptible and (2) Chloroquine resistant group. Base on the current guideline in U.S[1], three antibiotic regimens are employed for chloroquine resistant group (1) oral quinine plus either tetracycline, doxycycline or clindamycin, (2) atovaquone- proguanil and (3) mefloquine. Of all antibiotics, tetracycline, doxycycline, clindamycin, quinine and have been demonstrated to interact with the neuromuscular blocker. Mefloquine may interact with anticholinesterase agent.

Pharmacologic Interaction

Quinine

Quinine has been long known to possess neuromuscular blockade property[16-17]. The mechanism of neuromuscular blockade is secondary to inhibition of the phosphodiesterase activity in the skeletal muscle cytosol[18]. Quinidine, a close relative to quinine, has also been reported to interact with both depolarizing and non-depolarizing muscle relaxants to produce prolonged neuromuscular blockade[19-20].

Clindamycin

Clindamycin has been known to prolong neuromuscular blockade with non-depolarizing muscle relaxant, such as pancuronium and rocuronium. The prolonged effect is poorly responsive to calcium and reversal agent such as neostigmine[21].

Mefloquine

Mefloquine may interact with a number of anticholinesterase agents (e.g. physostigmine) to produce central anticholinergic syndrome[22]. If used independently, mefloquine may cause a number of neuropsychiatric symptoms such as anxiety, hallucination and depression.

Dapsone

Dapsone is a sulfonamide derivative used uncommonly in the treatment of malaria. It is typically used with pyrimethamine as chemoprophyaxis for malaria disease. It inhibits the synthesis of dihydrofolic acid by competing with para-aminobenzoate for the enzyme dihydropteroate synthetase. Clinically, dapsone causes methemoglobenemia. Reports involving intraoperative methemoglobinemia have

been made in patient who received dapsone for bullous lupus[23]. Pulse oximetry is typically inaccurate for the diagnosis of methemoglobinemia and co-oximetry is necessary in suspected cases intraopertatively.

Malaria in Transplant Surgery

Post-transplant diagnoses of malaria have been variously described in different literatures in cases involving liver, bone marrow and renal transplant[24]. In general, two mechanisms are responsible for transmission of malaria during organ transplantation: (1) blood product related (2) transmission of malarial parasites embedded in donor cells.

Therefore, chemoprophylaxis is routinely indicated in patients at endemic area.

Chemoprophylaxis in patients who receive cyclosporine should be done with caution. This is because quinine suppresses plasma cyclosporine level[25] while chloroquine may induce cyclosporine toxicity[26].

Malaria in Obstetric Patient

Malaria disease has been a usual cause of maternal death, miscarriage and preterm labor in the developing countries. However, little literature exists describing the implication of the disease in obstetric anesthesia.

Malaria disease in pregnancy is typically associated with heightened state of anemia, pulmonary complication and hypoglycemia[27]. This suggests that malaria during pregnancy may cause a higher mortality to both the mother and the fetus, and potentially aggravate anesthetic care.

Thrombocytopenia is commonly observed in this patient population. Therefore, performance of neuroaxial anesthesia should be accompanied by careful check of platelet count prior to the procedure. Theoretically spinal anesthesia may introduce malarial parasites from the blood stream into the spinal cerebrospinal fluid, causing cerebral malaria. However, this has not been proven clinically. Nonetheless, general anesthesia may be indicated in the situations of severe anemia, severe thrombocytopenia, fetal compromise and hemodynamic perturbation in the mother[5].

Chronic Pain in Malarial Patients

Chronic pain is relatively common in patients with malaria disease. Chronic headache is especially prevalent and as many as 80% of malaria infected patients present with headache[28]. It may be related to (1) cerebral malaria, (2) side effects of antimalarial drugs and (3) postmalaria neurologic syndrome.

Cerebral malaria should be ruled out prior to prescription of pain medication. Neurologic referral may be critical if cerebral malaria is suspected. Quinine toxicity or more commonly referred to 'cinchonism' may also cause headache. If necessary, referral for management of toxicity may be indicated.

Postmalaria neurologic syndrome is a poorly understood disease in patients recovered from malarial disease. Headache could present as one of the many symptoms. Steroids may be indicated in patients with severe, relapsing disease[29].

Conclusion

Malaria disease is still a significant disease in the beginning of the 21th century and it poses a significant healthcare burden to both the anesthetic team and non-anesthetic team alike. Understanding of the disease is therefore crucial for anesthetic management of patients with malaria. Further research is needed to fully disclose the anesthetic implication of the disease.

References

1. Griffith KS, Lewis LS, Mali S, Parise ME: Treatment of malaria in the United States: a systematic review. *JAMA;* 2007, 297:2264-77.
2. Newman RD, Parise ME, Barber AM, Steketee RW: Malaria-related deaths among U.S. travelers, 1963-2001. *Ann Intern Med*; 2004, 141:547-55.
3. Gibney EJ: Surgical aspects of malaria. *Br J Surg*; 1990, 77:964-7.
4. Gupta N, Lal P, Vindal A, Hadke Ns, Khurana N: Spontaneous rupture of malarial spleen presenting as hemoperitoneum: a case report**.** *J Vector Borne Dis*; 2010, 47:119-20.
5. Mathew DC, Loveridge R, Solomon AW: Anaesthetic management of caesarean delivery in a parturient with malaria. *Int J Obstet Anesth*; 2011, 20:341-4.
6. Idro R, Marsh K, John CC, Newton CR: Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. *Pediatr Res*; 2010, 68:267-74.
7. World Health Organization. Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster. *Trans R Soc Trop Med Hyg*; 2000, 94:S1-S90.
8. Ikumi ML, Muchohi SN, Ohuma EO, Kokwaro GO, Newton CR: Response to diazepam in children with malaria-induced seizures. *Epilepsy Res*; 2008, 82:215-8.
9. MUNGAI M, TEGTMEIER G, CHAMBERLAND M, PARISE M: Transfusion transmitted malaria in the United States from 1963 through 1999. *N Engl J Med*; 2001, 344:1973–1978.
10. Purohit M: Malaria and open heart surgery. *Asian Cardiovasc Thorac Ann*; 2003, 11:277-8.
11. Taylor WR, White NJ: Malaria and the lung. *Clin Chest Med*; 2002, 23:457-68.
12. Das BS: Renal failure in malaria. *J Vector Borne Dis*; 2008, 45:83-97.
13. Barsoum RS: Malarial acute renal failure. *J Am Soc Nephrol*; 2000, 11:2147-54.
14. Vaishnani JB: Cutaneous findings in five cases of malaria. *Indian J Dermatol Venereol Leprol*; 2011, 77:110.
15. Sundet M, Heger T, Husum H: Post-injury malaria: a risk factor for wound infection and protracted recovery. *Trop Med Int Health*; 2004, 9:238-42.
16. Moller KO: Action of quinine methochloride (methoquin) on neuromuscular transmission and its respiratory and cardiovascular actions. *Acta Pharmacol Toxicol (Copenh)*; 1946, 2:383-402.
17. Sieb JP, Milone M, Engel AG: Effects of the quinoline derivatives quinine, quinidine, and chloroquine on neuromuscular transmission. *Brain Res*; 1996, 712:179-89.
18. Shute JK, Smith ME: Inhibition of phosphatidylinositol phosphodiesterase activity in skeletal muscle by metal ions and drugs which block neuromuscular transmission. *Biochem Pharmacol*; 1985, 34:2471-5.
19. Kambam JR, Franks JJ, Naukam R, Sastry BV: Effect of quinidine on plasma cholinesterase activity and succinylcholine neuromuscular blockade. *Anesthesiology*; 1987, 67:858-60.
20. Schmidt JL, Vick NA, Sadove MS: The effect of quinidine on the action of muscle relaxants. *JAMA*; 1963, 183:669-71.
21. Al Ahdal O, Bevan DR: Clindamycin-induced neuromuscular blockade. *Can J Anaesth*; 1995, 42:614-7.
22. Speich R, Haller A: Central anticholinergic syndrome with the antimalarial drug mefloquine. *N Engl J Med*; 1994, 331:57-8.
23. Szeremeta W, Dohar JE: Dapsone-induced methemoglobinemia: an anesthetic risk. *Int J Pediatr Otorhinolaryngol*; 1995, 33:75-80.
24. Barsoum RS: Parasitic infections in transplant recipients. *Nat Clin Pract Nephrol*; 2006, 2:490-503.
25. Tan Hw, Ch'ng SL: Drug interaction between cyclosporine A and quinine in a renal transplant patient with malaria. *Singapore Med J*; 1991, 32:189-190.
26. Nampoory MR, Nessim J, Gupta RK, Johny KV: Drug interaction of chloroquine with ciclosporin. *Nephron*; 1992, 62:108-109.
27. Warrell DA, Molyneuz ME, Beales PF: Severe and complicated malaria. *Trans R Soc Trop Med Hyg*; 1990, 84:1.
28. Suyapuhn A, Wiwanitkit V, Suwansaksri J, Nithiuthai S, Sritar S, Suksirisampant W, Fongsungnern A: Malaria among hilltribe communities in northern Thailand: a review of clinical manifestations. *Southeast Asian J Trop Med Public Health*; 2002, 33:14-5.
29. Hsieh CF, Shih PY, Lin RT: Postmalaria neurologic syndrome: a case report. *Kaohsiung J Med Sci*; 2006, 22:630-5.