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Malaria at Chris Hani Baragwanath Academic Hospital Intensive Care Unit: Comparing outcomes between quinine and artesunate therapy.

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A research report submitted to the University of Witwatersrand, Johannesburg in fulfillment for the requirements of the degree of Master of Medicine, 2017.

DECLARATION

I, Rofhiwa Mathiba; hereby declare that this research is of my own work. I am submitting this research report for the degree Master of Medicine (in the submissible format with my protocol and extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. This research report has not been submitted before for any degree or examination at this or any other university.

RM Mathiba

(Signature of candidate)

21st day of November 2017 in Randburg

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To my husband, my two beautiful children and the rest of the extended family, a huge thank you for your unconditional love and support. I would not have achieved any of this without you.

SUBMITTED ARTICLE PENDING APPROVAL

1. Rofhiwa M. Mathiba, Lufuno R. Mathivha, Gladness D. Nethathe. Malaria at Chris Hani Baragwanath Academic Hospital Intensive Care Unit. Comparing outcomes between quinine and artesunate therapy. Original article submitted august 2017. Under review.

ABSTRACT

Background

Malaria is a preventable and treatable disease that is a major burden in the African sub-region, accounting for 75% of malaria related deaths globally. Prior to December 2009, quinine has been the therapeutic option of choice for the management of Malaria in our unit. In the non-intensive care unit setting a mortality benefit of artesunate over quinine has been shown by two major trials and thus artesunate is currently therapy of choice for severe malaria. There is paucity of South African data regarding the outcomes of severe malaria patients treated with quinine compared to those treated with artesunate in the intensive care unit (ICU).

Objectives

The aim of this study was to compare the outcomes of patients treated with artesunate versus those treated with quinine, over a four-year period in our ICU. The primary outcome variables were length of stay and mortality, secondary outcomes where hypoglycaemia episodes and neurological outcome as measured by GCS on admission and on discharge.

Methods

This was a retrospective cohort study of patients with severe malaria treated at Chris Hani Baragwanath Academic Hospital with artesunate or quinine. The study was done in an ICU setting. This included a review of patients treated in the unit from 1st January of 2008 to 31st December 2012. A p value of<0.05 was chosen as a measure of statistical significance.

Results

The sample consisted of 92 patients. Forty three percent (n=40) received quinine and 57% (n = 52) received artesunate. There was no statistically significant difference between the two drugs in the treatment of severe malaria in our ICU with regards to length of stay (p=0.738), mortality (p=0.246), hypoglycaemia (p= 0.246) and neurological outcome as measured by GCS on admission and discharge (p= 0.357).

Conclusion

In our intensive care population the difference in outcomes between artesunate and quinine were not statistically significant. Artesunate did not confer an obvious benefit over quinine. Considering the differences in cost, logistical differences associated with the use of the two drugs as well as the emergence of artesunate resistance, we suggest that outcomes of artesunate versus quinine be investigated in other non-endemic regions.

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ABBREVIATIONS

AIDS: Acquired immune deficiency syndrome

Apache II score: Acute Physiology and chronic health evaluation II score

ARDS: Acute respiratory distress syndrome

AQUAMAT: Artesunate versus Quinine in the treatment of severe falciparum malaria in African children.

CHBAH: Chris Hani Baragwanath Academic Hospital

GCS: Glasgow coma scale

HIV: Human Immunodeficiency Virus

ICU: Intensive Care Unit

MCC: Medicines Control Council

MODS: Multiple organ dysfunction syndrome

P. falciparum: Plasmodium falciparum

SA: South Africa

SEAQUAMAT: South East Asian Quinine Artesunate Malaria trial

SIRS: Systemic inflammatory response syndrome

SOFA score: Sequential Organ Failure Assessment score

TB: Tuberculosis

WHO: World Health Organisation

CHAPTER 1: PROTOCOL AND EXTENDED LITERATURE REVIEW

1.1 INTRODUCTION AND BACKGROUND

Malaria is a preventable and treatable disease that is a major burden worldwide and on the African continent. It is a protozoan infection, transmitted to humans by a blood-sucking female mosquito. There is a high prevalence of the disease in the tropical regions of the world such as Africa and Asia. The malaria pandemic continues in Sub-Saharan Africa, with increasing hospital admission statistics, despite great initiatives in disease prevention. In 2012, about 207 million cases were reported worldwide; the majority of which were in the Sub-Saharan region. The HIV pandemic in Sub-Saharan Africa adds to the overall disease burden, and poses a great risk of contracting severe form of malaria, especially for those that are non-immune.[1-2]

South Africa (SA) is noted as a low transmission area.[1] Transmission is usually in the rainy season, between October and May, with the spread of malaria being increased by travelers and migrant labour from neighbouring Sub-Saharan states. The provinces most affected are Limpopo, Mpumalanga and Kwazulu- Natal, although there has been a slight increase in the number of reported cases in the province of Gauteng.[3]

Malaria fevers have been described as early as 850 BC, by the early Greeks, and later on in 400 BC by Hippocrates. Hippocrates first observed patients with poor health, malaria fevers and enlarged spleens living in low lying wet areas.[4]

The search for the organism that caused malaria was only intensified in the 19th century by a French physician Alphonse Laveran, who then discovered the parasite in blood, also implicating mosquitos as vectors. At that stage, he could not describe how the disease was transmitted to humans. Only in the 1890s, did Ronald Ross discover an association between mosquitoes and birds infected by *Plasmodium Relictum.* This disease was termed avian malaria.
A hundred years later, Italian scientists finally confirmed the link between human malaria and mosquitoes.[4-5]

Malaria reached epidemic proportions in Africa around the 1990s resulting in the launch of the new global strategy in the year 2000.[6] Since then, the parasites causing malaria were identified as the Plasmodium species with many subtypes. The most common plasmodium species in the African continent, responsible for severe malaria is *Plasmodium falciparum* (*P. falciparum*). *Plasmodium vivax* also has the ability to cause severe malaria but is usually found in countries outside Sub-Saharan Africa.[7]

Non-communicable diseases such as ischaemic heart disease and stroke are the leading cause of death globally but in low income countries infectious diseases remain the leading cause of death. Sub-Saharan Africa carries a high burden of malaria related deaths, accounting for about 75% of deaths globally.[7] According to the global burden of disease report in 2004, malaria was number fourteen amongst the top leading twenty most frequent cause of death in the world. In low income countries, such as the African region, malaria was part of the top ten leading causes of death.[8] According to the World Health Organization (WHO), the malaria incidence has decreased by twenty nine percent globally between the period of 2010 and 2015. The global technical

strategy for malaria 2016-2030 aims to decrease the malaria incidence and mortality rates by at least 90 percent in 2030.[9]

1.2 LIFE CYCLE OF MALARIA

Only five species in the genus *Plasmodium* are known to cause infections in humans, namely *Plasmodium malariae*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium knowlesi* and *Plasmodium falciparum (P. falciparum)*.[10] *P. falciparum* is responsible for severe malaria and is associated with high mortality and morbidity. *P.falciparum* is accountable for 99% of malaria related deaths in Africa. The global incidence of *P.vivax* cases is about 4% and are most of this are seen outside the African continent.[11]

Transmission of malaria to humans begins when a female anopheles mosquito injects the parasite in the form of sporozoites, as it takes a blood meal from a human. The sporozoites travel through the bloodstream to invade hepatocytes. Over a period of 2 weeks they replicate to produce thousands of merozoites. Only *P. vivax & P. ovale* remain dormant in the hepatocytes for prolonged periods, where they can cause a relapse of the disease months to years later. The merozoites are released in the bloodstream to then invade the erythrocytes to develop into trophozoites and schizonts. Gametocytes develop once released from the erythrocytes and these are the infective stage for the mosquito. The lifecycle is complete when a mosquito then takes a blood meal, infecting the anopheles mosquito.[10, 12]

1.3 PATHOGENESIS OF MALARIA

P. falciparum primarily invades erythrocytes. The pathophysiology and clinical manifestations of malaria are, to a large extent, related to this erythrocytic invasion. The removal of infected erythrocytes by splenic macrophages results in the activation of the innate immune system and resultant release of cytokines. The infected erythrocytes adhere to vessel walls and to uninfected erythrocytes, resulting in interference with the microcirculation. This disturbance of flow and tissue perfusion can lead to ischaemic tissue injury.[10-13]

The release of cytokines also leads to expression of adhesion molecules by endothelial cells; this mediates parasite sequestration. Nucleic acids released from destroyed parasites activate toll-like receptors inducing the expression of interleukin-12 that promotes production of interferon gamma. Interferon gamma has a number of functions, with the primary function being to control parasite replication in the liver. Its other functions include recruitment of leucocytes; promoting opsonisation of infected erythrocytes and cytokine production.[12-13]

The consequences of these processes lead to persistent endothelial dysfunction promoting thrombosis; capillary leak with extravasation of fluid. Infected patients then present with two well-known manifestations of severe malaria, which are acute respiratory distress syndrome (ARDS) and cerebral malaria. Anaemia occurs due to haemolysis of infected and uninfected erythrocytes and cytokine-induced impairment of erythropoeisis. The release of oxygen free radicals and alteration in blood flow are responsible for the organ specific syndromes such as hypoxia, lactic acidosis, renal failure and cerebral malaria- features of severe malaria.[13 15]

1.4 SEVERE MALARIA IN THE INTENSIVE CARE UNIT (ICU)

1.4.1 Definition and Clinical Features of Severe Malaria

The WHO defines severe malaria as a complicated malaria infection, characterized by either organ failure or biochemical and haematological impairment.[16] In the early stages, the severity of disease can be masked by non-specific symptoms. Malaria is a mimicker of many conditions. When the disease becomes severe; severe anaemia, respiratory distress, metabolic acidosis secondary to acute kidney injury, non-cardiogenic pulmonary oedema and cerebral malaria occurs.[10, 14]

1.4.2 Management of Severe Malaria in ICU

The clinical manifestations of severe malaria and response to optimal ICU management is dependent on the infectious plasmodium species; host factors which include age, comorbid illnesses, previous immunity and pregnancy status. These are also used as predictors of poor outcome.[14]

The WHO has identified several preventative measures such as disease control using treated mosquito nets, chemoprophylaxis given to travelers visiting malaria endemic areas, surveillance with notification of all malaria cases and lastly eradication of malaria. These prevent the development of acute malarial infections with the associated high mortality and morbidity. These strategies however, do not impact the outcomes of patients with severe malaria in ICU, once they have contracted the disease. Therefore, patients with severe malaria need to be managed in an ICU with close monitoring. Severe malaria is a medical emergency with a high mortality if left untreated. [14]

1.4.2.1 Medical Therapy

Artesunate therapy

Artesunate is one of a number of anti-malarials derived from artemisinin, the active ingredient in a Chinese herbal remedy for fever known as *Artemisia annua.* Artesunate can be given intramuscularly or intravenously, reaching peak levels within the first hour of administration.[4] Artemisinin derivatives clear parasites faster and are observed to have a broader spectrum of activity than quinine. Importantly, they are effective in preventing the accumulation of young forms of the parasite in the microcirculation of vital organs and hence halt the progression to severe disease. Artesunate is the preferred drug of choice for treating severe malaria in the ICU. It has consistently shown superior anti-malarial properties especially in parasite clearance, with a good side effect profile.[2, 4, 17]

Artesunate is currently available through the parenteral artesunate access programme, developed by the Department of Clinical Pharmacology at the University of Cape Town, implemented in June 2009. The objective was to create access to parenteral artesunate by patients with severe malaria in South Africa (SA). Artesunate is not yet registered in SA with the Medicine Control Council (MCC) and is only available in terms of Section 21. In terms of this act, the MCC has authority with any transactions pertaining to artesunate and its use by persons and institutions. There are selected sentinel hospital sites based on their likelihood of treating most of the severe cases of malaria in South Africa. Chris Hani Baragwanath Hospital (CHBAH) in Gauteng is one of the hospitals administering artesunate to patients with severe malaria.[18]

In the non-ICU setting, the mortality benefit of artesunate over quinine has been shown.[2] The South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) was an open label, randomised trial, done on mostly adult patients with severe malaria. Patients were recruited and mostly managed in general medical wards. Few patients were in ICU. The trial was stopped early due to the substantial survival benefit in the artesunate group. Artesunate reduced mortality of severe malaria in Asian patients from 23.1% to 14.2%.[17]

The second biggest trial, artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT), was done in an African paediatric population. This was an open label, randomised trial conducted in nine African countries. Significant reduction in mortality in the artesunate group was found. These studies prompted the WHO to change its guidelines in advocating for the use of artesunate in patients with severe malaria.[2]

Artemisinin resistance is characterized by a delay in parasite clearance time. Artemisinin compounds derived from the plant *Artemisia annua* include artesunate, artemether and arteether. According to WHO definition, artemisinin resistance should be suspected in a population if more than ten percent of patients have not cleared the parasite in three days after the start of artemisinin based therapy.[19] There have been recent reports in Southeast Asia, confirming artemisinin resistance in five countries. A study done by White L.J et al. emphasizes the need for molecular markers to identify artemisinin resistance and the importance of the initial parasite load followed by another one done on the third day. Of interest is the current research in the *kelch 13 mutation*, which is found on the mutant parasite.[20] The cause of this resistance seems to be multifactorial, depending on drug factors, parasite factors as well host factors. It is

additionally not clearly defined how much parasite clearance is needed by day three. Combination therapy using two antimalarial drugs with different mechanism of action at the same time, has the potential to delay the development of resistance.[21]

Quinine therapy

For many centuries, quinine derivatives were the mainstay of treatment for all forms of malaria. There has not been much documented resistance to quinine as yet but the use of this drug is limited, mainly due to its unfavorable side effect profile. Quinine was discovered in the early 17th century and is it is a component of the bark of the Cinchona tree. Its antimalarial mechanism of action is unknown; however, it remains an important drug in the treatment of severe malaria. It has rapid schizonticidal action against intra-erythrocytic malaria parasites but no gametocidal effects on *P. falciparum*. It is well absorbed orally and parenterally. Quinine has a narrow therapeutic index and is associated with a number of devastating side effects which include vertigo, tinnitus, gastrointestinal disturbances and hypoglycemia. Hypoglycemia is a common side effect of quinine and occurs up to thirty-two percent of patients who receive this drug.[21-22]

Quinine is the oldest antimalarial to be discovered, and remains effective against falciparum malaria but sporadic cases of clinical failures were reported from South East Asia and South America.[23] The *Plasmodium falciparum* genome can encode multiple predicted polymorphisms in transport protein, predisposing it to resistance. These parasite transporters have an impact on different antimalarials and their responsiveness to the parasite. There are in vitro tests that suggest quinine resistance is associated with the following sodium transporter polymorphisms; plasmodium multidrug resistance protein -1(*PfMRP1),* plasmodium multidrug resistance-

1(*PfMDR1*), plasmodium falciparum chloroquine resistance transporter (*PfCRT*). When these three genes are present *P. Falciparum* is less responsive to quinine. Interestingly *PfCRT* is the molecular marker and primary mediator of chloroquine resistance.[24]

Quinine is structurally related to chloroquine but malaria parasites resistant to chloroquine are still sensitive to quinine. Resistance to quinine is less frequent in Africa, and in the last two decades the drug has been used in combination with doxycycline to enhance its effectiveness.[25]

1.4.2.2 Complications of severe malaria and supportive treatment in ICU

Acute respiratory distress syndrome

This is a complication that develops in about thirty percent of adult patients and more commonly in pregnant females. The development of ARDS is a poor prognostic sign. The indications for mechanical ventilation in patients with severe malaria is not different from any other medical conditions. This may include poor respiratory effort, ARDS, severe metabolic acidosis and aspiration pneumonia.[26] In the absence of mechanical ventilation mortality outcome exceeds eighty percent and with ventilation it can still exceed fifty percent, especially among patients infected with Falciparum.[13] The mechanism underlying ARDS is poorly understood but endothelial dysfunction and altered capillary permeability have been suggested as contributory. Treatment is the same as for any other cause of ARDS, which includes lung protective ventilatory strategies. Mechanical ventilation with lower tidal volumes, moderate to high positive end expiratory pressure are used to maintain oxygenation. Fluid balance is significant to monitor as fluid overload can exacerbate this condition.[27-28]

Co-infection and use of antibiotics

Bacterial co-infection should be suspected in patients with signs of sepsis, significant neutrophilia, rising C-reactive protein and a deteriorating clinical condition. Concurrent gram-negative non-typhoid salmonellae has been shown to be common in endemic areas especially affecting children. Other common affecting organisms include *Pneumococci, E.coli* and other gram-negative organisms. There should be a low threshold to the use of broad spectrum antibiotics.[26-27]

Renal failure, haemodialysis and fluid therapy

This is commonly seen as oliguric (<400ml/day) kidney injury in about sixty to seventy percent of cases.[13] The incidence is higher in non-endemic regions, while in endemic regions it varies from one to five percent. Histopathological findings are similar to those of acute tubular necrosis, although hypovolemia and haemolysis maybe contributory. The urine assessment is usually unremarkable, unless patients have "blackwater fever". This refers to a condition where a patient passes dark red or brown urine, secondary to haemolysis that then results in haemoglobinuria.[29] Blackwater fever can occur in patients treated with quinine, and may also be associated with glucose-6-phosphate dehydrogenase deficiency. It is usually transient, reflecting massive haemolysis and does not indicate severe renal impairment.[26-27]

Early renal replacement therapy, either haemofiltration or haemodialysis improves outcomes. The return of creatinine to normal, is a mean average of seventeen days.[13] Haemofiltration has proved to be superior when compared to peritoneal dialysis, especially in the ICU setting.[26] Trials of dopamine and epinephrine to improve renal outcomes have not been shown to improve

renal perfusion.[29] Quinine needs adjustment with renal impairment unless patient is on renal replacement therapy but there's no need for adjustment with artesunate.[29] The prognosis of acute kidney injury secondary to severe malaria is good.[27]

Fluid balance is an important issue in patients admitted with severe malaria to ICU. Aggressive fluid therapy is best avoided in these patients because of the risk of ARDS and cerebral oedema due to capillary leakage. A neutral fluid balance should be maintained for adequate systemic perfusion. A balance is critical to avoid precipitating acute kidney injury with a negative fluid balance. In case of hypotension, early use of inotropic support is indicated to prevent fluid overload.[27]

Neurological complications

Cerebral malaria is defined as a depressed level of consciousness, ranging from agitation, confusion, seizures or GCS below eleven that can't be explained by any other aetiology.[16] Cerebral malaria is usually complicated by cerebral oedema. It is associated with poor outcomes, despite the use of anticonvulsant therapy in patients with seizures. There are no adjunctive therapies that are currently recommended for cerebral malaria. There is no indication for the use of dexamethasone in cerebral malaria. Using steroids might prolong the period of coma as well as predispose patients to other side effects of steroids.[26-27]

Hypoglycaemia

This is defined as blood glucose less than 2.2mmol/l, this is particularly common in the paediatric population. This can be caused by parasite glucose consumption or impaired hepatic

gluconeogenesis in a patient with severe malaria. Hypoglycaemia maybe worsened by the use of intravenous quinine and can be avoided by regular monitoring and early enteral feeding.[26]

1.5 THE IMPACT OF THE MALARIA EPIDEMIC ON THE AFRICAN CONTINENT

Sub-Saharan Africa carries a high global burden of malaria cases. According to the WHO, about thirteen countries, mainly in Sub-Saharan Africa, account for seventy-six percent of malaria cases and seventy-five percent of malaria related deaths globally. Prevention and control strategies have led to twenty-nine percent reduction in malaria mortality rates since 2009.[7] The disease burden in African regions is further worsened by lack of resources, poor vector control measures and lack of access to treatment.[30] South Africa, however, has a relatively well-organized malaria control program and a relatively well-developed health infrastructure compared to our African counterparts.[31]

1.6 MALARIA INFECTION IN THE HIV INFECTED POPULATION

In Sub-Saharan Africa, 24.7 million people are living with HIV.[32] South Africa has the largest epidemic of HIV, and accounts for 17 percent of all AIDS related deaths in Sub-Saharan Africa. According to statistics SA, 16.8 percent of the population of adults aged between 15-49 years are estimated to be living with HIV.[33]

A link between HIV infection and severity of malaria has been demonstrated. A South African prospective study done by Cohen et al, showed that HIV infected non-immune adults are at an increased risk of severe malaria. This is associated with low CD4 counts.[34] This was further shown in studies in Malawi and Zambia which showed high risk of malaria re-infection in HIV

infected patients with CD4 counts less than 200. A prospective study done in Mozambique, which compared malaria infection in HIV versus non-HIV infected patients, revealed high morbidity and mortality in the HIV infected group. The mortality was twenty six percent in the HIV infected group versus nine percent in the non-HIV infected group. It must also be taken into consideration that this study was conducted in a malaria endemic region. [35-36]

1.7 PROBLEM STATEMENT

There is paucity of South African data regarding the outcomes of patients with severe malaria treated with quinine compared to those treated with artesunate in the intensive care unit. Bruwer et al at Tygerberg hospital in the Western Cape, a non-endemic area in South Africa, did a descriptive study reviewing the demographic, clinical and laboratory prognostic indicators of patients with severe malaria, in a tertiary intensive care unit.[6] However the sample size consisted of only sixteen adult patients and there was no comparison of the treatment modalities.

The SEAQUAMAT trial was done in South-East Asia, in a different setting to our study.[17] Soweto is a township, urban area with a high prevalence of HIV, a non-endemic area but high numbers of imported malaria from our neighbouring countries. This proposed retrospective study was conducted in an intensive care unit where patients received close monitoring, allowing for the observance of intensive care unit therapy on malaria. This will hopefully add to the growing body of evidence about the efficacy of artesunate in reducing severe malaria mortality in an intensive care unit setting.

1.8 AIMS AND STUDY OBJECTIVES

1.8.1 Aim of the study

The aim of this study was to compare the outcomes between patients treated with artesunate versus quinine. The study was done from 2008 to 2012 at Chris Hani Baragwanath Academic Hospital intensive care unit (CHBAH ICU).

1.8.2 Study Objectives

- To determine whether artesunate was effective in treating severe malaria when compared to quinine in an ICU setting.
- To assess and compare the APACHE II scores on admission of patients treated with quinine versus those treated with artesunate and the impact it had on the outcome.
- To compare the biochemical and haematological laboratory data of patients treated with quinine versus those treated with artesunate in ICU.
- To compare invasive and non-invasive interventions performed in ICU for patients with severe malaria treated with quinine versus those treated with artesunate therapy.

1.9 PRIMARY AND SECONDARY OUTCOMES

- Primary outcome measures were length of stay in ICU and in-ICU death or discharge from ICU.
- Secondary outcome measures were neurological status, as determined by level of consciousness (GCS) on admission and discharge as well as the number of hypoglycaemia episodes during ICU stay.

1.10 DEFINITION OF VARIABLES

- Travel history- a history of traveling outside of South Africa in the last 3 months.
- Comorbidities- concurrently present morbidities including HIV co-infection.
- SOFA score- Sequential organ failure assessment score, to determine the extent of a patient organ function or rate failure during ICU stay.
- APACHE II score- a scoring system designed to measure the severity of disease in patients admitted to ICU, applied within 24 hours of admission to ICU.
- Neurological status as defined by the admission Glasgow coma score (GCS). Participants were divided into three groups, participants with GCS of 0-11, 12-14 and GCS 15.
- Lactate level- participants were grouped and recorded into two groups; those with a lactate level more than 5 mmol/l and those with a lactate less than 5 mmol/l
- Parasite level of more than two percent was considered as significant in our study.
- Creatinine level on admission in mcmol/l
- Metabolic acidosis- defined as plasma bicarbonate level less than 15mmol/l.
- The need for inotropic support- was documented on the data collection sheet as YES or NO and cumulative doses were recorded.
- The need for mechanical ventilation - was documented on the data collection sheet as YES or NO.
- The need for renal replacement therapy- was documented on the data collection sheet as YES or NO.
- Hypoglycemia was defined as HGT level less than 2.2 mmol/l.
- Total length of stay in ICU- participants were grouped into three groups: less than 5 days stay in ICU, more than 5 days stay in ICU and the group within 5days.

- Neurological status was assessed using GCS on discharge, psychiatric or other focal neurological signs were noted.
- Arrhythmias during ICU stay – abnormalities of rhythm were documented.
- ICU outcome- was defined as in- ICU death or discharge from ICU.
- Non-invasive intervention - a diagnostic or therapeutic procedure that does not require incision through skin or insertion of an instrument to a body orifice.
- Invasive intervention - a diagnostic or therapeutic procedure that involves skin incision or penetration of a body orifice by using an instrument.

1.11 METHODS

1.11.1 Study Design

This was a retrospective cohort study of patients with malaria treated in ICU with artesunate and those treated with quinine. All admissions with severe malaria from the 1st of January 2008 to 31st of December 2012 were included.

1.11.2 Study setting

This study was conducted at CHBAH ICU. CHBAH is a three thousand bed academic hospital, affiliated to the University of the Witwatersrand in Johannesburg, South Africa. It serves mainly the community of Soweto but is also a referral hospital for most surrounding towns and other provinces. The internal medicine department is the largest and busiest in the hospital, comprising of about seven hundred and seventy-six beds.

1.11.3 Study Sample

The study sample included all patients who were admitted at CHBAH ICU with the diagnosis of malaria from the 1st January 2008 to 31st December 2012. All patients admitted to CHBAH ICU, fulfilling the WHO criteria for severe malaria, were included in the study. This included adult over or equal to the age of 18 years. The patients were treated with either quinine or artesunate therapy in ICU.

1.11.4 Data Collection

Patients admitted to Chris Hani Baragwanath hospital are logged into the ICU admitting book system with clear admission diagnosis and relevant demographic data. Details of all the patients with a diagnosis of severe malaria were obtained, these were correlated with their ICU files that are kept in the ICU records room. The artesunate book which has records for all patients who were admitted with severe malaria and received artesunate was used as a cross reference. The following flow diagram would further illustrate the sampling process.

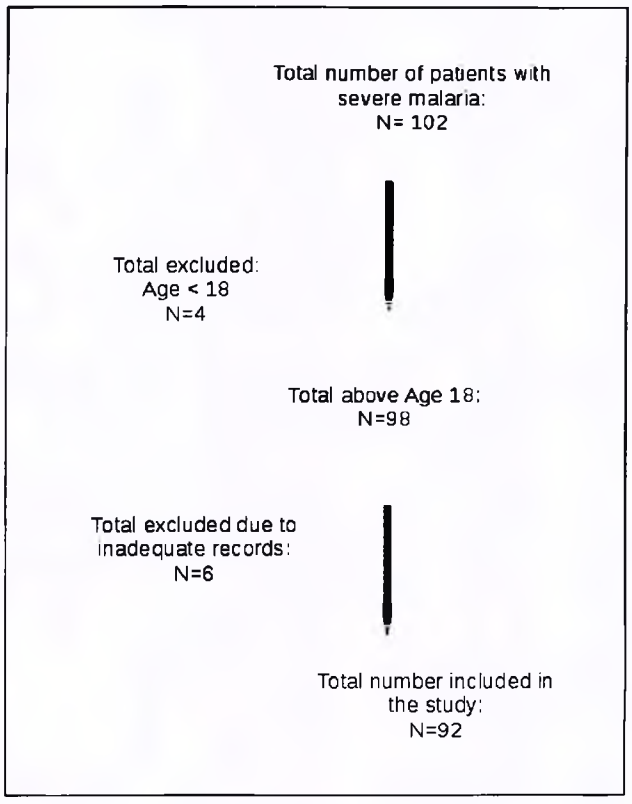

Figure 1: Study Participants

1.11.5 Statistical Analysis

The data collection sheet (Appendix B) was used for data collection. Data was analysed using STATA version 13, with the help of a statistician. Categorical variables were expressed using frequency distributions. Continuous data were expressed using mean, range and percentages. The statistical test that was used to compare the outcome of the two therapies in our study was the two samples student t-test. A p value of <0.05 was considered to be statistically significant.

1.12 LIMITATIONS

The following limitations of the study have been identified. The sample was small and may not be representative of the national group of critically ill patients with malaria. Therefore, results might not be generalized to most patients with severe malaria in ICU.

Bias may have occurred due to the retrospective nature of the study design. We had to rely on information that was available in the ICU charts. The other challenge was that the files are not kept in an electronic database, making it difficult to account for missing data. The possibility of inclusion bias exists, since ICU admission is often a clinician and management based criteria. The admission threshold may be different depending on the clinician requesting the admission and the intensivist assessing the request for admission. Resource limitation and ICU bed availability in our setting means some cases of severe malaria who may have required intensive care unit admission were treated in other wards such as the medical High Care Unit in our hospital or the obstetrics High Care Unit.

1.13 ETHICS

This was a retrospective review of data. All patients given artesunate in our unit had signed informed consent as part of MCC approval or consent had been obtained from a legal proxy. Ethics approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand as well as the University's Postgraduate Committee before commencement of the study (Ethics clearance certificate number: M50120). Permission was also obtained from the hospital management of CHBAH as well as the University of Cape Town's clinical pharmacology department to conduct this study.

Confidentiality of subject data was maintained at all times and subject anonymity was guaranteed. All documentation relating to the subject was kept in a secure location. The names and identification numbers of the patients were assigned a number on a restricted access excel document. Confidentiality was guaranteed in any resulting publication.

1.14 SCHEDULE

	Research & Protocol	Protocol Submission	Data Collection	Data Analysis	MMed Submission
06/2014					
11/2014					
03/2015					
02/2016					
07/2017					

1.15 FUNDING

No external funding was required.

1.16 REFERENCES

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CHAPTER 2: SUBMISSIBLE ARTICLE
MALARIA AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL INTENSIVE CARE UNIT: COMPARING OUTCOMES BETWEEN QUININE AND ARTESUNATE THERAPY.

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Short Title: Comparison of Artesunate versus Quinine in the treatment of Severe Malaria in ICU.

Conflict of Interest: Nil

Keywords: Artesunate, Quinine, severe malaria, ICU

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ABSTRACT

Background

Malaria is a preventable and treatable disease that is a major burden in the African sub-region, accounting for 75% of malaria related deaths globally. Prior to December 2009, quinine has been the therapeutic option of choice for the management of Malaria in our unit. In the non-intensive care unit setting a mortality benefit of artesunate over quinine has been shown by two major trials and thus artesunate is currently therapy of choice for severe malaria. There is paucity of South African data regarding the outcomes of severe malaria patients treated with quinine compared to those treated with artesunate in the intensive care unit (ICU).

Objectives

The aim of this study was to compare the outcomes of patients treated with artesunate versus those treated with quinine, over a four-year period in our ICU. The primary outcome variables were length of stay and mortality, secondary outcomes where hypoglycaemia episodes and neurological outcome as measured by GCS on admission and on discharge.

Methods

This was a retrospective cohort study of patients with severe malaria treated at Chris Hani Baragwanath Academic Hospital with artesunate or quinine. The study was done in an ICU setting. This included a review of patients treated in the unit from 1st January of 2008 to 31st December 2012. A p value of<0.05 was chosen as a measure of statistical significance.

Results

The sample consisted of 92 patients. Forty three percent (n=40) received quinine and 57% (n = 52) received artesunate. There was no statistically significant difference between the two drugs in the treatment of severe malaria in our ICU with regards to length of stay (p=0.738), mortality (p=0.246), hypoglycaemia (p= 0.246) and neurological outcome as measured by GCS on admission and discharge (p= 0.357).

Conclusion

In our intensive care population the difference in outcomes between artesunate and quinine were not statistically significant. Artesunate did not confer an obvious benefit over quinine. Considering the differences in cost, logistical differences associated with the use of the two drugs as well as the emergence of artesunate resistance, we suggest that outcomes of artesunate versus quinine be investigated in other non-endemic regions.

INTRODUCTION

Malaria is a preventable and treatable disease that is a major burden worldwide and more especially in the African sub-region. In 2012, about 207 million cases were reported worldwide. The majority of these were in the Sub-Saharan region.[1] The disease is more prevalent in the tropics, and despite preventative measures it remains a major reason for hospital admission in Sub-Saharan countries.[2] South Africa (SA) malaria transmission is seasonal and regional between October and May.[3-4]

Sub-Saharan Africa carries a high burden of malaria related deaths, accounting for about 75% of deaths globally.[5] Unfortunately, most of the mortalities occurs in the under-five age group, an age group more susceptible to severe malaria infection.[1] According to WHO the malaria incidence has decreased by 29% globally between the period of 2010 and 2015.[5] The global technical strategy for malaria 2016-2030, aims to decrease malaria incidence and mortality rates by at least 90% in 2030.[6]

In the non-ICU setting, studies have shown mortality benefit of artesunate over quinine.[2, 7] The South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) was an open label, randomised trial, involving 1461 patients with severe malaria. The mortality in the artesunate group was 15% compared to 22% in the quinine group (p=0.000). The trial was stopped early due to the substantial survival benefit in the artesunate group.[7]

The second biggest trial, artesunate versus quinine in the treatment of severe *falciparum malaria* in African children (AQUAMAT), was done in an African paediatric population. This was an

open label, randomised trial conducted in nine African countries, all malaria endemic regions. The primary outcome was in hospital mortality, 8.5% in the artesunate group compared to 10.9% in the quinine group, (p=0.002). Overall reduction in mortality in the AQUAMAT study was 22.5% (p=0.002). The results of these two trials prompted the WHO to change its guidelines and to advocate for the use of artesunate in patients with severe malaria.[2]

Challenges relating to the availability of artesunate was an initial barrier to its use in our hospital. Artesunate is not currently registered in South Africa. It is only available on a named patient basis via the parenteral artesunate programme, which was approved in 2009 for patients 12 years and older with severe malaria.[8]

Additionally, there is paucity of South African data regarding the outcomes of patients with severe malaria treated with quinine compared to those treated with artesunate in the ICU. South Africa (SA) is noted as a low transmission area, however malaria is endemic in three provinces of South Africa, Mpumalanga, Kwazulu Natal and Limpopo. Transmission is usually seasonal, between October and May, with the spread of malaria being increased by travelers and migrant labour from neighbouring Sub-Saharan states.[3-4] Gauteng, the region in which our study is set, is a non-endemic area. Furthermore, the two large trials AQUAMAT/SEAQUAMAT did not include patients managed in the ICU where close monitoring and one to one nursing is the standard.[2, 7] Close monitoring in an ICU setting allows for early detection and management of potential complications of the disease or therapy. Currently two studies have been done in South Africa, both looking only at prognostic indicators in a non-endemic area.[9-10]

The aim of the study was to compare outcomes between patients treated with artesunate versus those treated with quinine at CHBAH ICU. The primary outcome was the length of stay in ICU and mortality in patients with severe malaria who were treated with artesunate versus quinine. Secondary outcomes were assessing neurological status (assessing level of consciousness on admission and discharge) and number of hypoglycemic episodes (defined as a glucose level less than 2.2mmol/L) on the two therapies.

METHODS

The study was conducted at Chris Hani Baragwanath Academic Hospital ICU (CHBAH ICU). CHBAH ICU is a tertiary level ICU affiliated to the University of the Witwatersrand, in Johannesburg, South Africa. The hospital is located in the South-Western townships of Johannesburg (Soweto). Surgical and medical patients are both admitted into the unit and referrals come mainly from the community of Soweto as well as from peripheral hospitals in the surrounding towns and provinces. Soweto is classified as a low malaria transmission area. The malaria cases admitted into our unit are mostly travelers, who travel back from malaria endemic regions in the neighbouring regions.

Ethics approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand prior to commencement of the study (Ethics clearance certificate number M150120, approved 20/02/2015).

Study population and data collection

This was a retrospective cohort study of patients with severe malaria treated in ICU with artesunate and quinine. The study sample included all patients who were admitted to CHBAH ICU with the diagnosis of malaria whose files could be found in our records from the period of 01 January 2008 to 31 December 2012. These included adults aged 18 years or above, who met the WHO guidelines for severe malaria. There were no exclusion criteria. Details of all patients with a diagnosis of severe malaria from the ICU were obtained from ICU records. The following flow diagram further illustrates the sampling process.

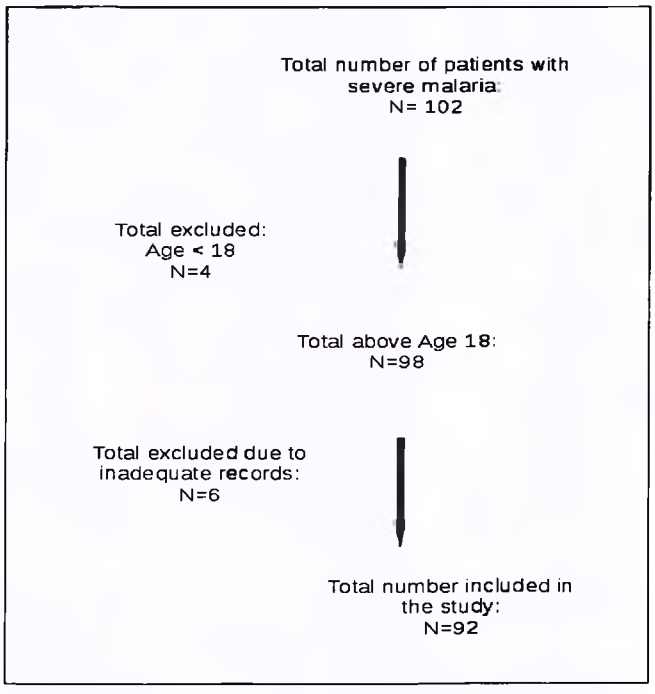

Figure 1: Study Participants

Statistical Analysis

Data analysis was conducted using STATA version 13. Categorical variables were expressed using frequency distribution, chi square test and t-test. Continuous data was expressed using descriptive statistics such as mean, range and percentages. The two samples t-test was used to compare the outcome of the two therapies. Probability levels of less than 0.05 were accepted as statistically significant.

RESULTS

Demographics

The sample consisted of 92 patients. There were 64 males and 28 females. Of the 92 patients, 43% (n = 40) received quinine while the other 57% (n = 52) received artesunate. The mean age of patients in the quinine group was 36 compared to 40 in the artesunate group (p =0.071). Most of the patients (98.6%) had a positive travel history to a malaria endemic region. Regarding HIV, 53 patients were tested, and of these 71.7% tested HIV positive while 28.3% tested negative (p=0.520). The average CD4 count of HIV positive patients treated with quinine (cells/mm^3) was 200, and was 217 for those treated with artesunate (p= 0.875). The sample distribution is shown in the following figure:

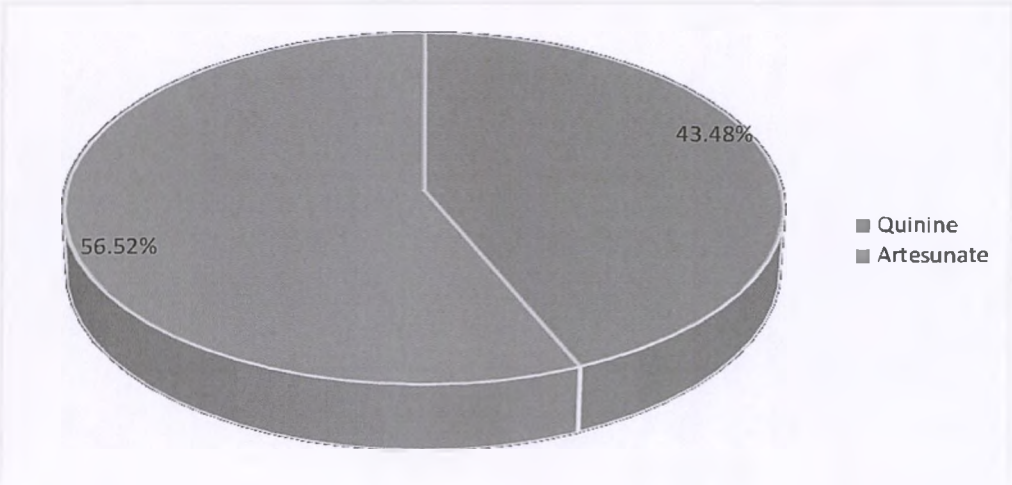

Figure 2: Antimalarial drug administered in ICU

Primary outcome

There was no statistically significant difference between the artesunate and quinine groups with regards to length of stay in ICU (p=0.738) and mortality (p = 0.246). With regards to patients admitted for less than five days, 45% (n=40) received quinine and 46.2% (n=52) received artesunate. With regards to patients admitted longer than five days, 42.5% (n=17) received quinine while 46% (n=24) received artesunate.

There was no significant association between the drug received and mortality (p = 0.246). A total of 10 patients died, those that received quinine, 84.6% (n=33) survived till discharge and 15.4% (n =6) died in ICU. With regards to the artesunate group, 89% (n=46) survived till discharge while 11% (n= 4) died in ICU.

Secondary outcomes

The mean Glasgow coma scale on admission in patients treated with quinine was 11.6 versus 12.4 in the artesunate group (p= 0.302). The mean GCS on discharge was 14.9 for patients administered quinine versus 14.1 for patients who received artesunate (p= 0.081).

Nine patients died in ICU with an overall mortality rate in ICU of 11%. The most common neurological complication was seizures accounting for 39.3% in the total sample (p= 0.357). The number of hypoglycaemia events were two (5.9%) in the quinine group compared to none in the artesunate group (0 %). The average blood glucose level (mmol/l) was 5.69 for patients treated with quinine and 6.41 for patients treated with artesunate (p= 0.596).

Biochemical and hematological tests

The mean parasite count in percentages for patients who received quinine was 0.12 and 0.14 for patients who received artesunate (p= 0.416). There was no difference in the mean bicarbonate level (mmol/l) on admission between patients who received quinine (17.2 mmol/l), and those who received artesunate (18.4 mmol/l) (p=0.241). The mean lactate level (mmol/l) for patients who received quinine was 5.23 and 4.37 for those who received artesunate (p= 0.291). Hemoglobin levels (g/dl) were similar with mean levels of 8.47 and 8.96 for those who received quinine and those who received artesunate respectively (p= 0.425). Creatinine (mcmol/l) on admission for patients using quinine were on average 300 and patients on artesunate therapy 390 (p= 0.187). The APACHE II score on admission was similar in the two groups, patients on quinine had an average of 20.85, while those on artesunate had an average of 19.62 (p= 0.380).

Invasive management

The duration of inotropic support on patients treated with quinine was on average 4.6 days compared to 3.5 days for those treated with artesunate (p= 0.423). There was no difference regarding the duration of renal support, those on quinine needed renal replacement therapy for an average of 6.0 days while those on artesunate had on average 6.6 days (p= 0.730). The average number of days needed for mechanical ventilation for patients treated with quinine was 5.5 days compared to 6.0 days for those patients treated with artesunate (p= 0.812).

Table 1: History and Clinical Data of patients on antimalarials in ICU

Variable	Categories	Quinine	Artesunate	Total	P-value
Gender	n	39	52	91	0.646
	Female	33.3%	28.8%	30.8%	
	Male	66.7%	71.2%	69.2%	
Travel	N	29	41	70	1.000
	Yes	100.0%	97.6%	98.6%	
	No	0.0%	2.4%	1.4%	
HIV	N	17	36	53	0.520
	Positive	64.7%	75.0%	71.7%	
	Negative	35.3%	25.0%	28.3%	
Comorbidities	N	12	10	22	0.201
	Pregnant	41.7%	10.0%	27.3%	
	Obese	0.0%	20.0%	9.1%	
	Hypertension	8.30	10.0%	9.1%	
	Asthma	0.0%	20.0%	9.1%	
	Previous TB	16.7%	0.0%	9.1%	
	Previous malaria	8.3%	10.0%	9.1%	
	Diabetes mellitus	8.3%	0.0%	4.5%	
	Ischaemic heart disease	8.3%	0.0%	4.5%	

	Chronic kidney disease	0.0%	10.0%	4.5%	
	Epilepsy	0.0%	10.0%	4.5%	
	Previous malaria & Epilepsy	0.0%	10.0%	4.5%	
	Hypertension & Benign prostatic hypertrophy	8.3%	0.0%	4.5%	
Inotropes	N	40	52	92	0.337
	Yes	67.5%	57.7%	62.0%	
	No	32.5%	42.3%	38.0%	
Renal support	N	40	52	92	0.495
	Yes	52.5%	59.6%	56.5%	
	No	47.5%	40.4%	43.5%	
Mechanical ventilation	N	40	52	92	0.023
	Yes	50.0%	26.9%	37.0%	
	No	50.0%	73.1%	63.0%	
Neurological complications	N	17	11	28	0.357
	Seizures	41.2%	36.4%	39.3%	
	Drowsy	17.6%	9.1%	14.3%	
	Pulmonary edema	0.0%	18.2%	7.1%	
	Vision loss	5.9%	0.0%	3.6%	
	Speech defect	0.0%	9.1%	3.6%	
	Psychosis	5.9%	0.0%	3.6%	
	ARDS	11.8%	0.0%	7.1%	
	Confusion	0.0%	9.1%	3.6%	
	Splenic infarcts	5.9%	0.0%	3.6%	
	Prolonged QT/ cardiac arrest	5.9%	9.1%	7.1%	
	Upper GIT bleeding	0.0%	9.1%	3.6%	
	Hypoglycaemic episodes	5.9%	0.0%	3.6%	
Length of stay	N	40	52	92	0.738

	<5 days	45.0%	46.2%	45.7%	
	Exactly 5 days	12.5%	7.7%	9.8%	
	> 5 days	42.5%	46.2%	44.6%	
Outcome	N	39	52	91	0.246
	Discharge	84.6%	92.3%	89.0%	
	Death	15.4%	7.7%	11.0%	

DISCUSSION

Malaria is a major cause of death in Sub-Saharan Africa. South Africa, specifically the Gauteng province, is considered a non-endemic region. However, there is an increasing number of cases of severe malaria associated partly to travellers from endemic areas entering South Africa.[4] In addition, South Africa has the highest HIV infection rate of any country in Africa making its citizens more susceptible to developing severe malaria as a result of immunosuppression.[3]

The average cost of parenteral artesunate is currently higher compared to quinine but however artesunate is cost effective, considering the reduction in mortality and shorter duration of treatment.[11] Advantages of artesunate are rapid antiparasitic activity and a shorter half-life. The duration of treatment is seldom required beyond three days, ease of administration and rapid clinical benefit. Parenteral artesunate is easier to administer compared to quinine. It requires once daily intravenous administration, compared to quinine that requires a loading dose and thereafter three times per day intravenous dosing. [12]

Treatment with artesunate is well tolerated with minimal side effects compared to quinine. The main adverse effects that have been reported since the initiation of the artesunate programme have been renal failure and haemolysis.[11] Quinine is associated with a number of side effects,

hypoglycaemia being one of the more common ones.[8] Parenteral quinine requires dose adjustment in patients with renal impairment, a condition frequently encountered in patients with severe malaria.[11]

The main disadvantage is that artesunate is not currently registered in SA. Access is only available on a named patient basis via the parenteral artesunate programme, which was approved in 2009 for patients 12 years and older with severe malaria.[8]

The World Health Organization (WHO) defines severe malaria as a complicated malaria infection, characterized by either organ failure or biochemical and haematological impairment. Severe malaria often requires admission to an ICU in order to manage complications of multi-organ failure.[13]

Several large studies have shown that artesunate is superior to quinine in the treatment of severe malaria.[2, 7] None of the studies comparing the two drugs were done in South Africa in an ICU setting. As mentioned before South Africa is a non-endemic region and despite the low transmission rate, the case fatality rate has remained unchanged in over a decade, at 0.76%, 0.26% above the WHO target of 0.5%. This could be due to a number of factors, such as delay in seeking treatment, delay in the diagnosis of malaria, co-morbid illnesses, ineffective treatment of uncomplicated malaria, adverse effects of therapy such as hypoglycaemia and fewer hospitals with ICU's. The ICU environment allows for detailed management, close observation as well as early detection of complications.[11]

Two studies have been done in an ICU setting in South Africa. Blumberg et al, at CHBAH ICU assessed predictors of mortality in severe malaria over a 2-year period (1993 to 1994). These were clinical and laboratory features that are used to define severe malaria according to the WHO. The study included 28 patients with severe malaria treated with quinine. The setting and study population was similar to our study. Pregnancy was found to be a major risk factor for poor outcome in this study, other parameters such as high APACHE II scores, high lactate and negative base excess within the first 24 hours of admission were also associated with poor outcomes.[10]

The second study was a descriptive study done by Bruwer et al, at Tygerberg hospital in the Western Cape, a low malaria transmission and non-endemic area in South Africa. They reviewed laboratory and clinical aspects of sixteen ICU patients with severe malaria. The mortality rate was 43.8% (n=7), and of interest, majority of the patients (93.8%) received quinine therapy.[9]

The sample size of these two studies was small and there was no outcome comparison between patients treated with quinine versus those treated with artesunate. In our study, we sought to investigate whether there would be an outcome different between patients treated with quinine versus artesunate in an ICU setting.

We found that there was no statistically significant difference between outcomes of patients with severe malaria in our ICU treated with artesunate and quinine in our study. Our findings are in contrast with results of two major trials SEQUAMAT and AQUAMAT which were however done in a different setting to ours. There were few factors which were different in our study;

Apart from the differences in study designs most of the patients in our study were HIV positive (57.6%), our study was set in a non-endemic environment and all our patients were treated in an ICU. This allowed for organ specific support interventions when necessary as opposed to the setting of the two major trials, wherein patients where mostly treated in general wards. There was no difference in the length of stay when using the different treatment modalities. This is consistent with results of the AQUAMAT trial, where the time to discharge was 3 days in both the artesunate and the quinine group (p= 0.059).[2, 7]

The mortality benefit seen with artesunate was greater in South East Asia compared to the African population. This may be because of less resistance to *P.falciparum* malaria in Africa to quinine.[2,7] In our study there was no statistically significant difference in mortality between artesunate and quinine (p= 0.246). Mortality in the quinine group in our study (15.4%) was much lower compared to a study done prior by Blumberg et al in our ICU (28, 5%). Reasons for this could be a difference in co-morbidities such as HIV co-infection in the two groups.

Consistent with our findings is a study done in India comparing the efficacy of quinine and artesunate in severe *P. falciparum* malaria. This was a prospective randomised trial, open label in a tertiary center and included 35 patients who met WHO criteria for severe malaria. Eighteen received quinine and 17 received artesunate. The end points were parasite clearance time, fever clearance time, coma resolution time, adverse effects of the drugs and death. All patients were admitted to general wards, except four patients with acute respiratory distress syndrome admitted to ICU. One patient died in each arm. Patients treated with artesunate had shorter times to fever

resolution and parasite clearance, while coma resolution was quicker in the quinine group. As with our study there was no mortality benefit of artesunate versus quinine in this study.[14]

We did not find any significant differences between neurological outcomes with the use of artesunate versus quinine. This is consistent with findings from the AQUAMAT trial where neurological sequelae were found to not be significantly different between artesunate and quinine. This finding has also been supported by other investigators. The development of convulsions, coma and the deterioration in the Glasgow coma scale score seems to be slightly higher in the quinine group.[2, 15] Further investigations to further evaluate this are warranted.

Hypoglycaemia is an important and treatable cause of death in severe malaria and is of multifactorial origin. This can occur on presentation and also during the course of treatment, mechanisms include impaired liver function in severe malaria leading to impaired gluconeogenesis and glycolysis and drug induced hyperinsulinaemia. In a recent Cochrane systematic review comparing artesunate versus quinine for treating severe malaria treatment with artesunate resulted in a significant reduction in mortality, parasite clearance and hypoglycaemia in patients with severe malaria in Asia. Artesunate appears to be associated with fewer hypoglycaemic episodes than quinine. The number of hypoglycaemia events documented on admission in our study were 5.9% in the quinine group compared to none in the artesunate group ($p = 0.357$). The proposed mechanism is inappropriate insulin release from the pancreatic beta cell. Hypoglycaemia has however been observed in severe malaria without treatment with quinine.[15-17]

The emergence of resistance to artesunate in South East Asia has been reported in a number of studies and is characterized by decreased parasite clearance times. The common mutation associated with artemisinin resistance to falciparum malaria in Asia is the PfKelch13 mutation.[18-21] There seem to be a few mutations emerging from Africa as recently demonstrated in a case report of a patient who contracted falciparum malaria in Equatorial Guinea and failed treatment with artesunate.[22-23] Resistance was not a focus of our study but this case report highlights the importance of continued access to therapeutic options to artesunate.

More than half of patients included in our study were HIV positive. HIV associated immunosuppression has been postulated to increase the risk of contracting malaria and reducing the efficacy of anti-malarial therapy. Interestingly HIV and malaria infection follow the same geographical distribution. The full extent of the pharmacokinetic interactions between anti-malarial and anti-retroviral drugs used in the management of HIV is scarce due to limited published data. Difficulty in distinguishing adverse reactions from antimalarial therapy versus those of antiretroviral therapy or from severe malaria infection itself may pose a diagnostic challenge. The increased incidence of severe malaria in HIV infected patients is likely to augment the overall burden of disease, increasing morbidity and mortality in Sub-Saharan African population.[24-25]

The current standard of care for the treatment of malaria is similar in HIV infected and non-HIV infected individuals. Data shows use of antiretroviral therapy might reduce the morbidity of severe malaria in HIV infected individuals.[26] Therefore early diagnosis and initiation of antiretroviral in our population can assist in reducing the morbidity and mortality associated with severe malaria. Further research is needed to clarify this in the future as well as the clinical implications of the use of antiretrovirals together with antimalarials.

Limitations encountered in our study was a small sample size that may not be representative of the national group of critically ill patients with malaria. Bias may have occurred due to the retrospective nature of the study design. The possibility of inclusion bias exists, since ICU admission is often a clinician and management based criteria. Resource limitation and ICU bed availability in our setting means some cases of severe malaria who may have required intensive care unit admission were treated in other units such as medical wards.

CONCLUSION

In our intensive care population the difference in outcomes between artesunate and quinine were not significant. Though our population had a high incidence of HIV co-infection, artesunate did not confer an obvious benefit over quinine. Artesunate is more expensive, not as easily accessible and furthermore, resistance to artemisinin combined therapy including artesunate is emerging. Quinine should thus continue to be considered a therapeutic option. We suggest that outcomes of artesunate versus quinine be investigated in other settings such as ICUs and non-endemic and population groups such as those with HIV co-infection.

List of figures:

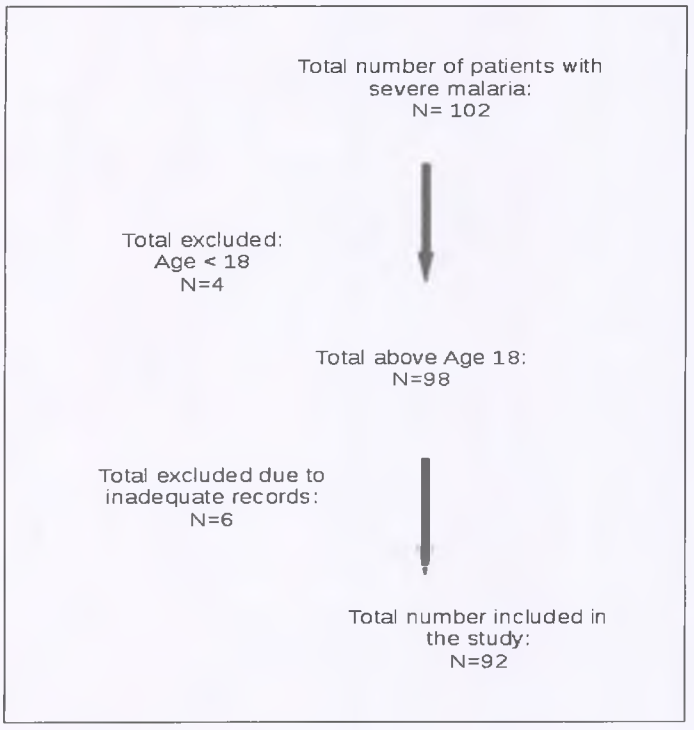

Figure 1: Study Participants

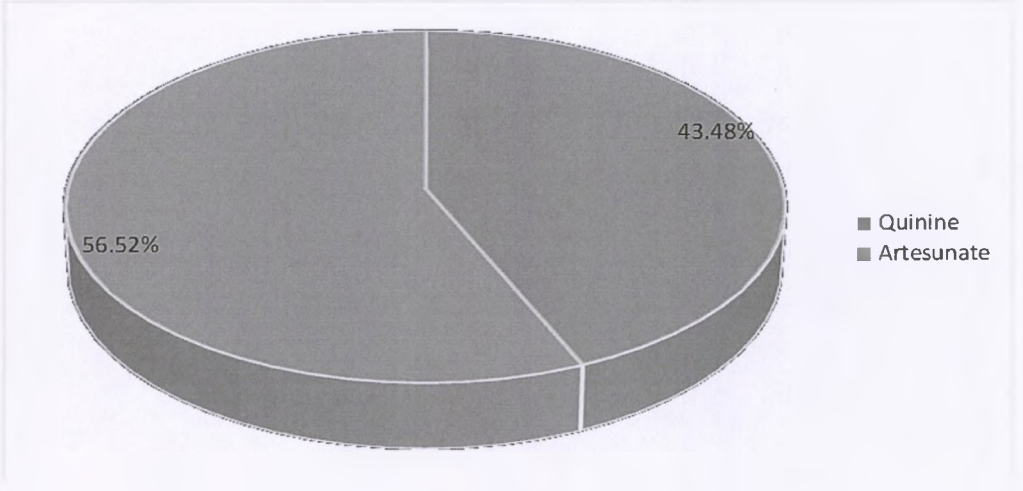

Figure 2: Antimalarial drug administered in ICU

Table 1: History and Clinical Data of patients on antimalarials in ICU

Variable	Categories	Quinine	Artesunate	Total	P-value
Gender	n	39	52	91	0.646
	Female	33.3%	28.8%	30.8%	
	Male	66.7%	71.2%	69.2%	
Travel	n	29	41	70	1.000
	Yes	100.0%	97.6%	98.6%	
	No	0.0%	2.4%	1.4%	
HIV	n	17	36	53	0.520
	Positive	64.7%	75.0%	71.7%	
	Negative	35.3%	25.0%	28.3%	
Comorbidities	n	12	10	22	0.201
	Pregnant	41.7%	10.0%	27.3%	
	Obese	0.0%	20.0%	9.1%	
	Hypertension	8.30	10.0%	9.1%	
	Asthma	0.0%	20.0%	9.1%	
	Previous TB	16.7%	0.0%	9.1%	
	Previous malaria	8.3%	10.0%	9.1%	
	Diabetes mellitus	8.3%	0.0%	4.5%	
	Ischaemic heart disease	8.3%	0.0%	4.5%	
	Chronic kidney disease	0.0%	10.0%	4.5%	
	Epilepsy	0.0%	10.0%	4.5%	
	Previous malaria & Epilepsy	0.0%	10.0%	4.5%	
	Hypertension & Benign prostatic hypertrophy	8.3%	0.0%	4.5%	
Inotropes	n	40	52	92	0.337
	Yes	67.5%	57.7%	62.0%	
	No	32.5%	42.3%	38.0%	

Renal support	n	40	52	92	0.495
	Yes	52.5%	59.6%	56.5%	
	No	47.5%	40.4%	43.5%	
Mechanical ventilation	n	40	52	92	0.023
	Yes	50.0%	26.9%	37.0%	
	No	50.0%	73.1%	63.0%	
Neurological complications	n	17	11	28	0.357
	Seizures	41.2%	36.4%	39.3%	
	Drowsy	17.6%	9.1%	14.3%	
	Pulmonary edema	0.0%	18.2%	7.1%	
	Vision loss	5.9%	0.0%	3.6%	
	Speech defect	0.0%	9.1%	3.6%	
	Psychosis	5.9%	0.0%	3.6%	
	ARDS	11.8%	0.0%	7.1%	
	Confusion	0.0%	9.1%	3.6%	
	Splenic infarcts	5.9%	0.0%	3.6%	
	Prolonged QT/ cardiac arrest	5.9%	9.1%	7.1%	
	Upper GIT bleeding	0.0%	9.1%	3.6%	
	Hypoglycaemic episodes	5.9%	0.0%	3.6%	
Length of stay	N	40	52	92	0.738
	<5 days	45.0%	46.2%	45.7%	
	Exactly 5 days	12.5%	7.7%	9.8%	
	> 5 days	42.5%	46.2%	44.6%	
Outcome	N	39	52	91	0.246
	Discharge	84.6%	92.3%	89.0%	
	Death	15.4%	7.7%	11.0%	

Table 1: Chi-square test for association between drug administered and several categorical variables

Table 2: Differences between the mean for patients on quinine vs those on artesunate

Variable	n	Quinine	Artesunate	Total	T	P-value (2-tailed)
Age	91	36.23	40.45	38.59	-1.825	0.071
CD4 Count in cells/mm^3	15	200.00	217.17	213.73	-0.161	0.875
Duration of inotropes treatment in days	35	4.62	3.50	3.91	0.812	0.423
Duration of renal support in days	51	6.05	6.60	6.37	-0.347	0.730
Mechanical ventilation duration in days	34	5.55	6.00	5.74	-0.240	0.812
GCS on admission	92	11.65	12.44	12.10	-1.039	0.302
GCS on discharge	83	14.91	14.16	14.47	1.779	0.081
Parasite count in percentages	75	12.57%	14.90%	13.91%	-0.818	0.416
Lactate level in mmol/l	85	5.23	4.37	4.76	1.066	0.291
Bicarbonate level in mmol/l	92	17.20	18.49	17.93	-1.179	0.241
Heamoglobin level in g/dl	92	8.47	8.96	8.75	-0.801	0.425
Blood glucose level in mmol/l	87	5.69	6.41	6.09	-0.531	0.596
Creatinine level in mcmol/l	92	300.35	390.04	351.04	-1.329	0.187
APACHE II SCORE points	92	20.85	19.62	20.15	0.882	0.380

Table 2: Independent samples t-test for difference between the mean for patients on quinine compared to those on artesunate

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CHAPTER 3: APPENDICES

3.1 Data Collection Sheet

Study no:	
Age:	
Gender:	
Date of admission:	
Date of discharge/death:	
Drug administered (quinine/artesunate):	
Travel history **o yes** **o no**	
HIV status **o yes** **o no**	
Comorbidities **o 1** **o 2**	
Inotropic support **o yes** **o no**	**If yes, for how many days?**
Renal replacement **o yes** **o no**	**If yes, for how many days?**
Mechanical ventilation **o yes** **o no**	**If yes, for how many days?**
Neurological status **o GCS admission: (<11) (11-14) (15)** **o GCS discharge: (<11) (11-14) (15)**	
Length of stay in ICU: (>5days) (<5days)	
Parasite count on admission in percentages	
Lactate on admission in mmol/l	
Bicarbonate on admission in mmol/l	
Haemoglobin level on admission in g/dl	
HGT level on admission in mmol	
Creatinine in mcmol/l on admission	
APACHE II SCORE on admission	

3.2 APACHE Score Sheet

Physiologic Variable		+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)		≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mm Hg)		≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate		≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory Rate (nonventilated or ventilated)		≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation (mmHg) a. $FiO_2 > 0,5$ use $A\text{-}aDO_2$ b. $FiO_2 \leq 0,5$ use PaO_2	a	≥500	350-499	200-349		<200				
	b					> 70	61-70		55-60	<55
Arterial pH		≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium (mmol·l)		≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum Potassium (mmol·l)		≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (mg/dl, Double point score for acute renal failure)		≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)		≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count (in 1000/mm³)		≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow-Coma-Scale (GCS)		Score = 15 minus actual GCS								
Serum HCO_3 (venous, mmol·l, use if no ABGs)		≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
A = Total Acute Physiology Score APS		Sum of the 12 individual variable points								

B = Age Points

≤44 years	0 points
45-54 years	2 points
55-64 years	3 points
65-74 years	5 points
≥75 years	6 points

C = Chronic Health Points

If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows:

a. For nonoperative or emergency postoperative patients – 5 points

b. For elective postoperative patients – 2 points

APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic Health points)

(From: Knaus WA. Draper EA. Wagner DP. Zimmerman JE. APACHE II: a severity of disease

3.3 Ethics Clearance Certificate

R14/49 Dr Rofhiwa Mathiba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150120

NAME: (Principal Investigator)	Dr Rofhiwa Mathiba
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Malaria at Chris Hani Baragwanath Academic Hospital Intensive Care Unit: Comparing Outcomes Between Quinine and Artesunate Therapy
DATE CONSIDERED:	30/01/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Gladness Nethathe
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/02/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES