CMCH AND MORU: A HIGHLY SUCCESSFUL COLLABORATION

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Abstract

Chittagong Medical College and Hospital (CMCH) in Chittagong, Bangladesh, and Mahidol-Oxford Tropical Medicine Research Unit (MORU) of Bangkok, Thailand, are partners in a highly successful and productive research collaboration that is now heading into its tenth year. It produced arguably one of the most important clinical trials in tropical medicine this decade,

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the South-East-Asia-Quinine-Artesuante-Malaria-Trial (SEAQUAMAT) study, and has continued to evolve and grow ever since. The collaboration has successfully completed a number of significant clinical studies which have given important new insights into the management and pathogenesis of malaria and, to date, generated 14 peer-reviewed international journal publications. With each passing year, the size of the collaboration continues to increase along with the number and complexity of research studies undertaken. It has also helped to provide valuable postgraduate training to develop clinical services and increase capacity for high quality research in Bangladesh. The partners have complementary knowledge, skills and expertise and share common goals and it is hoped that this will remain a highly successful collaboration long into the future.

In 1979, a research collaboration was established between Mahidol University in Bangkok (Thailand) and the University of Oxford (UK), supported by the Wellcome Trust. Now known as the Mahidol-Oxford Tropical Medicine Research Unit (MORU) it is a Wellcome Trust Major Overseas Programme and its administrative offices and laboratories are located in Mahidol University's Faculty of Tropical Medicine in Bangkok. MORU undertakes clinical and laboratory studies on the epidemiology, diagnosis, pathophysiology and treatment of malaria, melioidosis, scrub typhus, leptospirosis and other tropical infections both in rural Thailand and in other countries in Asia and Africa.

For the first two decades, MORU's clinical and pathophysiology studies on severe malaria were principally on the Eastern and Western borders of Thailand. However, with increasing national prosperity and a successful malaria control programme, the incidence of malaria in Thailand fell steadily throughout this period. In contrast, in Bangladesh, where falciparum malaria had almost disappeared in the early 1990s, there was a substantial resurgence of the disease. In 2001 Professor Nick White, then Director of MORU, received an invitation from Professor M. Abul Faiz,

the then head of the Department of Medicine at Chittagong Medical College Hospital (CMCH) to visit Chittagong to discuss a possible collaboration on future studies of severe malaria. CMCH is the teaching hospital of Chittagong Medical College (CMC) and as the major tertiary referral government hospital on the edge of the malaria endemic Chittagong Hill Tracts, CMCH received large numbers of cases of severe malaria. The two professors quickly realized that they shared common goals and that a research collaboration would be mutually beneficial to both institutions. Thus a group of physicans from CMCH, the Malaria Research Group, embarked on what would turn out to be a highly successful collaboration with MORU.

Soon after this meeting, CMC and MORU began planning two collaborative research projects on severe malaria. The first was a randomized placebo-controlled trial of adjunctive treatment with the antioxidant N-acetylcysteine (NAC)[1]. This was completed in 2007 and it was found that, although systemic oxidative stress is increased in severe malaria, NAC had no effect on clinical outcome. The other project was an observational study which used orthogonal polarized light spectroscopy to measure the rate of blood flow in the rectal mucosa in patients with severe malaria. Extensive macrovascular obstruction was observed and this was proportional to the severity of the malaria. This was the first direct demonstration in vivo of the important role that microvascular obstruction plays in the pathogenesis of severe malaria[2].

Whilst these studies were in progress, the MORU research group and its collaborators were planning a large multicentre treatment study of severe malaria, the SEAQUAMAT study. This was a randomized trial of intravenous artesunate versus intravenous quinine and, as its primary outcome measure was mortality, large numbers of patients would be required. Recruitment began in 2003. In all, 1461 patients were recruited in four countries, Myanmar, West Papua, India and Bangladesh. Of those enrolled the largest number from a single site (453) was from CMCH. It was found that treatment with intravenous artesunate reduces mortality from severe malaria by 34.7% compared to quinine.[3] SEAQUAMAT was published in 2005 and as a result, the 2006 WHO Malaria Treatment Guidelines included for the first time a change in recommended first line therapy for severe malaria of artesunate in place of quinine. Both Professor White and Professor Faiz were members of the Technical Guidelines Development Group of the WHO [4]. Ever since, with the assistance of MORU, CMCH has been one of the few hospitals in the world to use intravenous artesunate to treat patients with severe malaria. A similar study is now underway in African children.

Following SEAQUAMAT, another project investigated the potential role of a new diagnostic technique for malaria, loop-mediated isothermal polymerase chain reaction (LAMP). It demonstrated that LAMP is possible in settings with limited technical resources with a sensitivity equivalent to microscopy and rapid diagnostic tests, but a lower specificity. Suggestions to improve the technique were made in the associated journal article [5]. CMCH was also a major source of data for another study conducted from 2003-2005. Data collected from 1050 patients (396 from CMCH) showed that age is an independent risk factor for a fatal outcome in severe malaria and presenting syndromes depend on age. The incidence and strong prognostic significance of coma and acidosis were similar at all ages in this study [6].

Uncomplicated malaria has been the subject of two studies resulting from the collaboration. In 2006-2007, a randomized trial of supervised versus non-supervised treatment with artemether/lumefantrine for the treatment of uncomplicated P. falciparum malaria enrolled 320 patients in Bandarban District Sadar Hospital. The efficacy of this treatment was found to be high and similar for supervised and non-supervised administration [7]. In another study by the collaboration, analysis of malaria screening results collected from 1999-2006 in the south of Chittagong District showed annual parasite incidence rates (API) of 8.4/1000 persons and suggested malaria incidence was much higher than officially reported for this area. It also demonstrated a large decrease in positive cases since 2003. The highest incidence of malaria was found to be in young adults, consistent with occupational exposure, although the highest rate of testing symptomatic patients for malaria was in children, suggesting significant numbers of adult cases may be being missed [8].

In 2006, a formal Memorandum of Understanding between CMC and MORU was signed between Professor Emran Bin Yunus, the then Principal of CMC, and Professor Nicholas J White, Chairman of Wellcome Trust South East Asian Tropical Medicine

Research Units; and the studies on severe malaria continued to expand. A detailed study in 2006-2007 of 21 patients receiving intravenous artesunate for severe malaria found this drug to have no significant adverse effects on the heart. In particular it did not prolong the electrocardiographic QT interval. This is another important advantage of artesunate over quinine in the treatment of severe malaria[10]. In 2008, a study of 171 patients investigating the causes of the hyponatraemia seen in the majority of patients with severe malaria found that it was associated with preserved consciousness and decreased mortality. This was thought likely to be due to selection of patients without coma that can continue oral hypotonic fluid intake in the setting of hypovolaemia. It was concluded that hyponatremia is not caused by SIADH and requires no therapy beyond rehydration [9].

Due to the large number of very unwell patients with severe malaria at CMCH, to assist with the development of the new Intensive Care Unit, in 2008 MORU helped organize annual training for medical and nursing staff by specialists from the UK and the Netherlands. This highly successful programme is ongoing and new initiatives are underway to provide similar training in renal medicine and ophthalmology. To assist with building capacity for research at CMCH, MORU has provided training in International Conference on Harmonisation Good Clinical Practice (GCP) with 30 attendees successfully completing the first course in 2009. Staff from MORU spend 3 months each year in the malaria season doing fieldwork in close partnership with staff from CMCH. Both groups continue to benefit greatly from the resulting exchange of knowledge and experience.

Studies of malarial retinopathy using direct ophthalmoscopy had previously been undertaken at CMCH with variable results. In 2007, collaborative studies began on malarial retinopathy. These began with a study to compare findings by nonexpert direct and indirect ophthalmoscopy in patients with malaria. This is now nearing completion. Since 2008, for the first time in patients with malaria, high resolution portable retinal photography has been used as an objective method to record retinal findings. This enabled the full spectrum of the unique, and sometimes subtle, retinal changes seen in malaria to be captured. These studies are ongoing and so far have found malarial retinopathy to be present in around two thirds of adults with cerebral malaria and that the severity of retinopathy correlates with the severity of malaria in this group[11,12]. Using this technique, the role of microcirculatory obstruction in the central nervous system in cerebral malaria is being investigated[13].

Other studies that are ongoing include a randomized trial of levamisole as adjunctive therapy in severe malaria and a randomized trial of the timing of enteral feeding in severe malaria.

To date, the collaboration between CMCH and MORU has generated 14 publications in international peer-reviewed journals[1-3, 5-15], and several more are in preparation.

Bangladesh is going to have its national institute of Tropical Medicine in Chittagong, the Bangladesh Institute of Tropical and Infectious Diseases (BITID). Meanwhile a road map has been prepared by scientists, including from both CMCH and MORU. BITID will provide a structure to further strengthen the collaborative studies.

Now nearing its 10th year, the collaboration between CMCH and MORU has contributed important new knowledge on the pathogenesis and treatment of malaria as well as helped to provide valuable postgraduate training to develop clinical services and increase capacity for research in Bangladesh. With each passing year, the size of the collaboration continues to increase along with the number and complexity of the projects undertaken. The partners have complementary knowledge, skills and expertise and share common goals and it is hoped that this will remain a highly successful collaboration long into the future.

Conflicts of interest

None declared.

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