The use of placebo in a trial of rectal artesunate as initial treatment for severe malaria patients en route to referral clinics: ethical issues

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ABSTRACT

Placebo-controlled trials are controversial when individuals might be denied existing beneficial medical interventions. In the case of malaria, most patients die in rural villages without healthcare facilities. An artesunate suppository that can be given by minimally skilled persons might be of value when patients suddenly become too ill for oral treatment but are several hours from a facility that can give injectable treatment for severe disease. In such situations, by default, no treatment is (or can be) given until the patient reaches a facility, making the placebo control design clinically relevant; alternative bioequivalence designs at the facility would misrepresent reality and risk incorrect conclusions. We describe the ethical issues underpinning a placebo-controlled trial in severe malaria. To protect patients and minimise risk, all patients were referred immediately to hospital so that each had a higher chance of prompt treatment through participation. There was no difference between artesunate and placebo in patients who reached clinic rapidly; among those who could not, a single artesunate suppository significantly reduced death or permanent disability, a finding of direct and indirect benefit to patients in participating villages and elsewhere.

DILEMMA

Patients die when they deteriorate from malaria, can no longer take oral medicines and are several hours from health facilities. If intravenous infusions of quinine cannot be given, quinine should be administered as a deep intramuscular injection (diluted to between 60 and 100 mg/ml), at a loading dose of 20 mg/kg (divided with half injected in each anterior thigh) followed by a maintenance dose of 10 mg/kg every 8 h.[1] It is not recommended by WHO outside a healthcare facility that can provide parenteral medications safely,[2] as it must not be given by unskilled staff and needs sterile equipment. Given as an intramuscular injection in the gluteus or where technique and sterility are compromised, it risks inadvertent nerve damage,[3–5] tetanus[6 7] and HIV transmission. The earliest that patients can obtain quinine is on arrival at a clinic; many die before they reach this facility, or they arrive having further deteriorated and die from complications, or survive sometimes with sequelae.

A single artesunate suppository can be given by minimally trained persons in remote settings. It substantially reduces *Plasmodium falciparum* parasitaemia,[8] but its clinical benefit was uncertain. It was developed for a new indication as prereferral therapy—to bring forward the time of treatment for patients who could not access injectable medication. But its deployment as prereferral treatment for severe malaria would be difficult without robust evidence supporting policy decisions to reprogramme funds towards early community-based care. With no other therapy physically possible (and treatment based on a presumptive diagnosis of malaria), a placebo-controlled trial to obtain evidence of clinical benefit was clinically relevant and reflected routine practice. To achieve reliable results and ensure that all participants obtained best care, the intervention chosen was treatment (artesunate or placebo) plus referral to the nearest hospital. The design was controversial.

CONTEXT

The prevailing patterns of healthcare and management of patients with severe malaria in rural communities were assessed in a 2-year preparatory phase during which information was obtained on malaria hospital admissions, malaria mortality and health-seeking behaviour of patients during life-threatening malaria episodes and fatal febrile illnesses. Underutilisation, long delays and under-referral of patients to facilities in severe illness were common before the intervention. In Bangladesh, only 12% of patients with acute illnesses used government facilities;[9] 85% of admitted hospital patients had been prostrated for more than a day before admission; postadmission mortality averaged 6.2%.[10] Frequent shortages of essential medicines deterred patients from attending facilities.[11] In Ghana, average distances to Navrongo clinics were long, 82% of severe malaria patients were admitted to hospital 1–3 days after the onset of the illness, and 5% died on admission. Most patients with danger signs—convulsions, altered consciousness and coma—were taken first to traditional healers.[12] In Tanzania, 84% of deaths occurred at home, and half the patients died without contact with medical care.[13] Common presentations of severe malaria were treated by traditional healers or were perceived untreatable using modern medicine; this compounded delays.[12 14 15] For financial reasons (costs of transporting the dead) seriously ill patients

were often not taken to hospital or sought premature discharge.[13]

The high proportion of patients who died without contact with the health system reflected a lack of confidence in the health system, difficult access to and shortage of medicines, poor referral and high transport and medical costs.

APPROACH

A multicountry, randomised placebo-controlled community-based trial was conducted in 149 study areas in Bangladesh, 45 villages in Ghana and 107 in Tanzania.[16] A large number (417) of community-based recruiters were trained to identify patients (with clinically suspected malaria who could not take oral medication) early in the evolution of the disease, to randomise them to a single dose of rectal artesunate or identical placebo, and immediately refer each patient to a medical facility for confirmation of diagnosis and continued management. Seventy-four field supervisors visited the recruiter every few days to maintain quality of work. Emphasis was put on provision of referral advice, and referral slips were provided to the nearest medical facility to encourage compliance with referral advice. The aim was to achieve faster and higher referral rates of patients so that each randomised patient would have a higher chance of prompt treatment and survival through participation.

Ethics clearance and data safety monitoring committee

Permission for the trial was sought from the Ministry of Health and through national ethics review processes in each country, from the ethics and research committee of the WHO and, in the vernacular, from the communities and from patients or their guardians prior to treatment. A Data Safety Monitoring Committee reviewed the study conduct, data and all serious adverse events, and never considered the interim results conclusive.

Community permission and participation

Detailed dialogue was initiated with communities, discussing the study aims and methods with village leaders, which included information on the drug, its efficacy and safety, rationale for the use of placebo, the requirement of signing or fingerprinting a consent form prior to treatment when an individual was ill, and the importance of proceeding urgently to hospital to complete treatment. The individual consent form was discussed in detail, and the form provided for review so that caretakers would be familiar with it in an emergency. The purpose was to inform the communities and to establish whether the villagers agreed to participate in the study, and be treated by village recruiters residing in their villages. The continual presence of village recruiters in study villages would maintain community awareness about the importance of early treatment and emphasise compliance with the advice to proceed to clinic.

Reducing delays

The study teams identified traditional healers (often the first choice for consultation for patients with altered consciousness or convulsions) and provided them with information on the study and study drug,[17] and sought their voluntary collaboration. Arrangements were made to enable traditional consultation before, or sometimes after, enrolment so that patients were identified early, treated and referred to clinics.

Hospital arrangements

No change to routine management of patients at hospital was made. In Asia, two blood slides were taken at randomisation and one provided to the patient together with a referral form (to identify the study patient as entitled to free hospital care and admission for at least 24 h), and arrangements were made to ensure availability of necessary medications or referral to a secondary or tertiary hospital for specialised management. In Tanzania, patients were provided with a referral slip identifying them as a study child; their entitlement to free hospital care was reinforced. In Ghana, three-wheeled motorised transport was stationed at primary health centres to transfer patients to the district hospital.

Informed consent and monitoring

Before the study initiation, the trialists and monitors verified that all trained village recruiters could perform their tasks under regular supervision. Thereafter all informed consents were checked, and households of patients were randomly visited by trial investigators and monitors to check that all procedures had been followed.

Results

The trial of rectal artesunate plus referral to clinic versus placebo plus referral to clinic took 10 years, from the beginning of the preparation phase to publication of results.[16] Almost 18 000 patients were treated and referred to clinic, but the main finding is based on one-sixth of these patients because some 5000 did not have a positive blood smear for malaria, a further 1000 had just been injected with an antimalarial drug, and 9000 quickly followed the referral advice they had been given and reached a clinic where antimalarial injections could be given. Among the 3000 patients who had a delay of more than 6 h (median 15 h) in reaching a clinic, early treatment with rectal artesunate prevented mortality and risk of serious, permanent CNS damage by approximately half (1.9% vs 3.8%, absolute gain 1.9%). As only three-quarters of all patients (ie, those with malaria) were analysed, the absolute gain among all patients who were several hours from clinic would be only about 1.4% (ie, three-quarters of 1.9%).

Because of rapid hospital referral, malaria mortality and morbidity decreased even without prereferral treatment: in Asia, there was 98% compliance with referral advice to proceed to hospital, a rapid transfer of patients to the nearest facility (median 2 h) and a reduction in hospital mortality from 6.2% before the trial[10] to 1.2% during the trial. In Africa, compliance with referral advice was 88%, and transfer of patients to a clinic occurred in a median of 4 h.[16]

The risk of death or disability varied substantially between each site, from around 2% to 8%, with an overall mean of 4% in the context of very high compliance with referral advice to proceed to hospital. Where the background risk of death or disability is higher than in the study and referral even more difficult, the absolute benefit would be considerably greater than was observed in the study.

DISCUSSION

The central and fundamental ethical dilemma in human experimentation is the balance between individual and community interest, especially when the stakes are high. The classic example is an emergency in which a clinical trial could determine potential therapeutic benefit for many people but poses a high risk for individual patients. At one extreme, the placebo is considered unethical when beneficial standard treatment exists;[18 19] on the other hand, placebo-controls are essential to protect society from ineffective medical interventions[20 21] or treatments.[22 23] All international guidelines have a

placebo-control as an option, even when proven treatment exists, although clarifications for its justification vary and can be contradictory.[24] The CIOMS 2002 and WMA 2008 guidelines now require the research to be a health priority of the population but guide against placebo-controls except where no current proven intervention exists, when a comparator would not yield scientifically reliable results[25] and on the condition that patients will not be subject to any risk of serious or irreversible harm.[26] Some guidelines anticipate that placebo use may be required in poor settings where logistics or economics preclude an active comparator.[24 25] That individual welfare takes precedence over public benefit is not contested, but science has been regularly accused of using placebo-control designs for self-serving purposes,[27 28] because a new drug has a chance of being superior, which can be demonstrated with fewer patients, at less cost.[29] In the last decade, there has been heightened sensitivity to research in which patients were allocated placebos in medical studies conducted[27 28 30–34] or planned[35] in developing countries, provoking spirited debates on standard of care, a proliferation of guidelines,[36–38] revisions and clarifications of placebo-control clauses[25 26] and new requirements for clinical trial registration.[39] The debates have increased public awareness about differences in health systems, recognition that research and development is least concentrated in or directed towards the benefit of developing societies where the burden of many diseases is greatest, that patients in these societies are often deprived of medication and healthcare commonly available elsewhere[34–40] and that medications constitute only one component of patient management.[41 42]

Our study therefore took place during a decade of keen interest in raising the ethical bar for clinical trials in resource-poor settings.[29 35 41] The study population comprised patients with suspected severe malaria, with symptoms requiring urgent referral (convulsions, inability to drink, vomiting everything, unconsciousness or lethargy) who could not take medication orally and who were not at a clinic where injections could be given. Alternative therapy was not an option. The standard (parenteral) route of administration of antimalarials in severe disease could not be used. In remote malarial areas, trained personnel and sterile conditions cannot be guaranteed, and risk to the patient has often occurred when technique is compromised.[3–7] For this reason, current practice is referral to the nearest facility for injectable treatment; the test drug was developed to provide effective therapeutic cover while patients are in transit.

For practitioners and policy-makers, the fundamental question was whether an effective antimalarial (given earlier than injectable medication) could benefit patients who have no alternative because of their remote location, or whether it would cause harm. A bioequivalence design at the clinic might have been relevant if the goal was to replace injections, but the objective was not substitution of existing therapy but bringing forward time of treatment for those who die or incur sequelae because they cannot get to clinics quickly. Phase II and III studies had been conducted with comparative designs to establish safety and efficacy of a single dose over 24 h,[8 43] and although results were promising, these patients did not represent the clinical condition of the target population prior to arrival at clinic.

A placebo-controlled study design in evolving severe malaria in remote communities was not chosen or undertaken lightly. The decision to conduct such a trial was not easy and was taken after careful deliberation by national and international groups, after field experience in rural communities, community permission and ethical approvals. There was no disagreement on the importance of the subject or that a comparator simply could not be given in the community safely. Controversy lay in resolving the ethical dilemma; the intervention was considered by some as unethical (because the informed consent might be doubtful: Would a placebo be understood by rural illiterate communities? Would mothers in the emergency situation understand the meaning of informed consent? Would placebo or artesunate patients be complacent and not follow referral advice—increasing or postponing mortality?) or because the results were predictable (artesunate kills parasites) but considered by others as essential to understanding safety and efficacy of an investigational drug in the population of interest in conditions of use. Scientists, policy makers and malaria experts gave careful consideration to all options in context, balancing and weighing arguments on whether the trial should be done, judging whether the risk—benefit could be predicted without the trial and whether a reasonable risk-averse patient living in these rural areas would knowingly and willingly agree to be randomised in the trial.

Rapid diagnostic tests for malaria were not commonly available at the time of the study, and the trial treatment was provided on the basis of a clinical diagnosis of malaria. The pretrial low referral rates and long delays in seeking hospital care were of concern; absence of follow-up management would place all patients at risk and erode any early gain. Furthermore, the danger signs of severe malaria are similar to those of other diseases such as bacterial pneumonia, sepsis or meningitis, and patients might have concurrent anaemia, diarrhoea or malnutrition. Although a blood slide was taken for later parasitology in most patients, until laboratory diagnosis was made it could not be assumed that the treated patient had malaria; the proportion of malaria patients among those who had similar symptoms would vary with time, season and location. Consequently, referral to clinics was added as an extra intervention to treatment with artesunate or placebo to give all who entered the trial the benefits of clinic management. Emergency treatment at the hospital needed emphasis in the community; artesunate provided on the basis of a clinical diagnosis would not necessarily benefit all patients but was not anticipated to harm those without malaria.

The trial involved children with severe malaria; thus, efforts were made to eliminate any risk and to provide as much direct benefit to each patient as possible. All participants received referral to the facility and were provided with standard therapy at facilities on arrival. To mitigate the anticipated poor adherence to referral advice to go to facilities, there was a 2-year preparation period in which capacity was built at the community level to understand the rapid progression of malaria, the symptoms associated with evolving severe malaria, the importance of early treatment and referral, and the nature of the trial to take place. The trialists trained village recruiters to treat and refer all treated patients to clinics, provided referral slips to patients and introduced strong incentives to reach clinics quickly.

As a result, all who entered the trial received an intervention that was better than would have been available in the absence of a trial. Guardians of patients were aware of procedures and the informed consent long before the emergency, so that when they presented for treatment with a severely ill patient, their decision was made; this gave meaning to the informed consent process and reduced the time of counselling and consenting during the emergency. These efforts were not essential to a placebo-controlled study but were an obvious mechanism for minimising risk, improving community information, encouraging diagnosis

and improving patient prognosis and survival. As a result, the majority of patients (92%) complied with referral advice; indeed, three-quarters of all patients reached a clinic that could provide standard treatment within 6 h,[16] making trial-associated improvements in community organisation and in the health system more important than the intervention in these patients.

Had referral not been emphasised, patient mortality would likely have been much higher, and the trial shorter; referral narrowed the difference between treatments. In Asia it was shown that if villages could be organised to recognise and rapidly refer suspected cases of severe malaria to hospitals that provide good, affordable emergency treatment, cure rates would be far higher than was previously the case in these areas, and mortalities would be far lower. This was good for the patients and their families during the trial, particularly in improving their access to services in ways that could be maintained by the health system, benefiting the communities as a whole beyond the individual benefits. Health system improvements lowered death rates. The approach focusing on the community and the health system and not merely on the medication responded to the broader moral backbone of ethical guidelines rather than their clauses.[41] The interim results of the trial were never considered conclusive by the Data Safety Monitoring Committee, but the final results are conclusive, and will eventually be of direct and indirect benefit to future patients in the participating villages and elsewhere. There is work ahead. Information from a controlled deployment study and on economic aspects of the intervention are now being analysed to provide real-life evidence on how the drug can be distributed and made available in remote locations. Rectal artesunate is being developed as an inexpensive generic product for which marketing approval is being sought. Policy makers will need guidance, cost information, training materials and the benefit of long experience in building capacity in remote locations. Meanwhile, reliable evidence for policy has emerged from a placebo-controlled trial in which patient welfare was a primary consideration.

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Competing interests AF and FB are on the WHO Antimalarial Treatment Guidelines Committee.

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