European Journal of Integrative Medicine 20 (2018) 90–97

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/locate/eujim

Clinical trial

Adjunctive moxibustion treatment for tuberculosis: A randomised clinical trial investigating potential efficacy and comparative safety

Hood Ahmed Ibanda[a], Frank Mubiru[a], Rogers Musiba[a], Sachiko Itaya[b], Jenny Craig[b], Merlin Young[b], Paul Waako[a,c,*]

[a] Department of Pharmacology and Therapeutics, Makerere University, Kampala, Uganda
[b] Moxafrica, United Kingdom
[c] Busitema University, Mbale, Uganda

ARTICLE INFO

Keywords:
Moxibustion
Tuberculosis
HIV
MDR-TB
Immuno-modulation
Immunotherapy
Randomised control trial

ABSTRACT

Introduction: Small cone direct moxibustion ('moxa') is known to have been used in Japan at the height of its tuberculosis (TB) epidemic in the pre-antibiotic era with documented reports of efficacy including one scientific animal study. Antimicrobial resistant (AMR) disease is becoming a major threat to global health with drug-resistant TB the largest component of this threat, most particularly in Africa and Asia. This study comprises the first scientific investigation into whether this simple traditional therapy might help the challenge of reducing the persistent burden of TB in middle- and low-income countries.

Methods: 180 newly diagnosed TB patients were randomly assigned to two groups, one given standard first line ‘Directly Observed Treatment, Shortcourse' (DOTS) TB drug therapy, and the other first line DOTS along with daily self-administered moxibustion. The two groups were carefully monitored for differences in recovery rates and serological and immunological markers were compared.

Results: The moxa group responded to the drug therapy faster than the group receiving standard TB therapy as measured by their becoming sputum negative (P = 0.032 in the first month). There were accompanying improved haemoglobin levels of statistical significance (P = 0.003) with the same P value seen in a sub-group of TB patients who were also HIV positive. It was also noted that the moxa patients reported statistically significant better adherence to their drug therapy (P = 0.001).

Conclusions: The results demonstrate positive effects of moxa treatment on both reduced infectivity and drug adherence including in HIV co-infected cases. Despite previous reports of a wider range of haematological effects, these were limited to an increase in haemoglobin. There was no evidence that moxa use led to improvements in patients' well-being, contrary to previous anecdotal evidence.

The paper concludes that more investigations should be developed to provide a broader understanding of both effect and potential benefit of moxa therapy in treating human pulmonary TB disease (both with and without co-infection with HIV). It further recommends that these should include MDR-, XDR-, (multi-drug resistant and extensively-drug resistant) and programmatically-untreatable TB (including in palliative care scenarios).

1. Introduction

1.1. Background

Tuberculosis (TB) is one of the leading killer diseases in developing countries. Caused by *Mycobacterium tuberculosis* it can affect any part of the body (most commonly the lungs) and its concomitant risks are closely associated with both socio-economic factors and weakened host immunity [1]. TB itself was officially declared a global emergency by WHO in 1993. A quarter century later, the pandemic has yet to be brought under control in many middle- and low-income countries: in fact nearly 2 million are still dying each year (with a case fatality ratio of over 20% in Africa) and there are now estimated to be over 10 million annual new cases of active disease [2].

Antimicrobial resistant disease (and particularly drug-resistant TB) is well recognised as posing a major threat to global health, particularly where resources are poor [3,4]. A clinically and diagnostically distinct portion of the TB pandemic has been designated as multi-drug resistant TB (MDR-TB)

* Corresponding author at: Department of Pharmacology and Therapeutics, Makerere University, College of Health Sciences, Box 7072, Kampala, Uganda.
E-mail address: pwaako@chs.mak.ac.ug (P. Waako).

https://doi.org/10.1016/j.eujim.2018.04.006
Received 12 December 2017; Received in revised form 23 April 2018; Accepted 24 April 2018

(i.e. strains which are resistant to at least the two strongest first line drugs) which has been officially described by WHO as having become a new 'crisis' on its own account [5]. Currently it is estimated that 600,000 new cases of MDR-TB are occurring each year with "about 240,000" of these dying annually (i.e. roughly a 40% case fatality ratio) [6]. Furthermore a recent review on global antimicrobial resistance predicted that 75 million lives will have been prematurely lost just to this drug-resistant part of the pandemic by 2050, with 2.5 million a year then dying just from MDR-TB (i.e. a tenfold increase on existing levels) [7]. New drugs and vaccines are being investigated, but an effective new vaccine is considered unlikely in the near future [8], and new drugs, besides being expensive and immensely difficult to manage in resource-poor environments, will inevitably result in fresh drug-resistance (which has already been seen with both of the two recently approved new drugs Bedaquiline and Delamanid) [9]. Under such challenging circumstances it is recognised that alternative approaches are needed [10,12]. This study investigates patient response to one such intervention.

Several studies have underscored the role of the immune system in the containment of TB infections [1,10,14–17]. It is therefore conceivable that immuno-modulators may have therapeutic potential in the prevention and treatment of tuberculosis, particularly if they are proved to be safe and simple to administer although it is reported that no clinically useful innovations are yet on the horizon [11]. Moxibustion (moxa) has been widely believed to improve immune response and is also a very simple treatment.

Moxibustion has been used in Japanese and Chinese traditional medicine for at least two millennia to treat a multitude of illnesses including tuberculosis [18]. This therapy involves repeated application of brief heat to specific points on the body. A variety of approaches have been used and described as moxibustion. In this study the specifically Japanese tradition was utilised, using tiny pieces of moxa floss (dried and refined leaves of mugwort – *Artemisia princeps*). The moxa floss is smouldered on the skin so that the patient feels the heat [18] with the dosage varied according to the health of the patient and the severity of the condition being treated [19]. The smoke from this style of moxa therapy (using small cones) has been demonstrated to be generally safe [20]. Documentary records from the 1930s state that moxa was used successfully for the treatment of TB in Japan before the advent of TB drugs including one animal study which demonstrated its potential clinical effects under controlled conditions [21]. Research from that time and more recently [22] has consistently suggested that the very slight and locus-specific heat damage caused by moxa in the dermal layers can stimulate a range of immune responses.

The moxa floss that was used in this study was the highly refined 'White Fuji' moxa from the Sennenkyu company of Japan. The regimen for small cone moxibustion used was the one recommended by the Moxafrica charity [23]. Moxafrica is a UK based registered charity founded to investigate whether small cone direct moxa might play a positive role in combatting the growing pandemic of drug-resistant TB in the coming years (www.moxafrica.org). The charity provided financial support for this study.

1.2. Objectives

WHO has set a goal to eradicate TB by 2035 with one of the strategies being to intensify research directed towards finding new effective and affordable treatments [24]. The current study set out to test the null hypothesis that use of adjunctive moxa with standard WHO-approved drug treatment for TB would produce no measurable differences in effectiveness when compared with the use of standard drug regimen alone.

2. Methods

2.1. Trial design

The study was an open-label randomised controlled clinical trial phase IIb, managed from a single TB clinic in Uganda. 180 newly diagnosed TB patients were randomly assigned to two equal parallel groups, to receive either standard (2HERZ/4HE)[1] Category I first line drug treatment (as a control) or the same standard treatment with the addition of daily self-administered moxibustion.

2.2. Participants and ethical approvals

The study was carried out with permission from Research and Ethics committee of the School of Biomedical Science at Makerere University, Kiswa Health Centre II and the Uganda National Council for Science and Technology (UNCST). Informed consent of the patient was sought using a written consent form that was both in English and the local Lugandan language. The benefits and possible risks of participating in the study were carefully explained, patient confidentiality guaranteed and it was also made clear that participating in the study was not a prerequisite for receiving care from Kiswa Health Centre. Patients participating in the study, together with their attendants, were given clear instructions in moxibustion therapy, techniques and requisite safety measures.

Eligible participants were all aged 18 or over with newly diagnosed sputum positive TB who met the eligibility criteria for Category I TB treatment according to the Ugandan national TB treatment guidelines. Exclusion criteria were pregnancy, previous diagnosis of tuberculosis, diabetes, and patients already under immune modulating therapy (steroids or hydroxychloroquine).

Patients were included in the study regardless of HIV status (which was automatically checked at enrolment). This was deliberate because HIV is recognised as being a frequent confounder for successful TB treatment and because little is known about response in HIV patients to small cone direct moxibustion. These patients were especially carefully monitored in the early stages for any exacerbation of signs and symptoms of disease.

2.3. Study setting

The study took place at Kiswa Health Centre, one of ten public primary health care facilities operated by Kampala Capital City Authority which offer outpatient services including smear microscopy and DOTS TB treatment. As of 2015, the estimated Ugandan HIV prevalence among adults (aged 15 to 49) stood at 7.1% but this is believed to be higher in city areas [25]. Uganda is a designated high burden country in respect of both TB and HIV with the most recent incident rate for TB estimated as being 201/100,000 (42% of whom are also HIV positive) [2].

2.4. Interventions and their implementation

All patients in both treatment groups received standard TB regimen in exact accordance with national guidelines. The anti-TB drugs were supplied by the government of Uganda to the study centre and were used according to WHO recommendation. Adherence to medication was then also monitored throughout the study.

The study group (as an adjunct to their drug therapy) applied daily moxa bilaterally on an acupuncture point on each of their legs (St36, *zu san li)*. This is an acu-point point with a well-documented record of stimulating host immunity [26]. This daily treatment was self-administered by the patients. The cone sizes were prepared by the patients from the moxa floss supplied by the study team to be approx. 1 mg in weight (otherwise described to the patients as needing to be loosely rolled into a shape resembling half a grain of dried rice). Each cone was then lit by means of a smouldering taper supplied to the patients by the

[1] 2 months daily Rifampicin, Isoniazid, Pyrazinamide and Ethambutol followed by (subject to successful sputum conversion) 4 months daily Isoniazid and Ethambutol.