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.

study nurse. The moxa was snuffed out by the patient a few seconds after lighting as soon as he/she felt any heat.

The patients on adjunctive moxibustion were trained in its administration at the start of their drug therapy by the designated TB nurse, and were given medication counselling covering both anti-TB treatment and possible moxibustion side-effects. Moxa application as used in the study is described in detail on the website https://www.moxafrica.org/copy-of-uganda-project-1.

Before leaving from the first visit, the moxa patients were asked to self-administer moxa in the presence of the study nurse and to complete it to her satisfaction. They were then instructed to self-administer it on a daily basis. Patients were instructed to begin using three cones at each point each day, increasing to a maximum daily dosage of seven cones. Patients were instructed to discontinue moxa therapy and to contact the centre if they believed they were suffering any ill-effects from the moxa.

Individual patient safety was regularly monitored both by the senior study nurse (who was not blinded to the allocation of patients) and by the study doctor (who was blinded) and whose decision in the event of stopping therapy would be final. No patients were stopped for this reason.

2.5. Outcomes

The primary outcome measure was sputum conversion. Since sputum microscopy remains the gold standard for diagnosis of TB in Uganda this was considered to the most useful measurement of outcome. Other measurements included full blood counts, radiological analysis (intended to be the subject of a second paper) and renal and hepatic function for reasons of patient safety. Well-being was also measured using the Karnofksy scoring method, conducted by patient interview with the designated study doctor who was blinded to the status of the patient.

The well-being outcome measure was set as either achieving normal daily functioning (a Karnofsky score 80 or more) or a clinically significant improvement in functioning (a change in Karnofsky score of 20 or more) by the end of treatment.

2.6. Changes to outcomes

There were no changes to outcomes.

2.7. Sample size

The sample size was chosen using the formula for sample size estimation in a randomized control trial: $N = 2\ [(z1\text{-}\alpha + z1\text{-}\beta)/(d\text{-}\ \delta 0)]\ 2P\ (1\text{-}P)$. The study was designed to have a power of 0.8 and $\alpha = 0.05$, using a response rate of 70% based on WHO reports. A loss-to-follow-up rate of 5% was estimated.

2.8. Randomisation generation, type, concealment mechanism, implementation and blinding

Participants were randomly assigned following a simple randomization procedure to 1 of the 2 treatment groups, one group all treated with standard TB drugs, the other treated with standard TB drugs and adjunctive daily moxa. A total of 180 identical envelopes were prepared with designations of either moxa or no-moxa clearly identified on paper within them. These envelopes were in no specific order and each patient was asked to choose an envelope by the senior study nurse, as a result of which the patient was inducted into one of the groups and then monitored by the study nurse accordingly.

Since almost all outcome measurements were remotely made by scientific measurements there was considered to be no reason for more complex randomisation. The study doctor (who conducted Karnofsky assessment and adherence questionnaires) was blinded and was never present at the randomisation.

2.9. Statistical methods

The data was analysed using STATA version 13.0, Texas, USA. Baseline characteristics were described using frequencies, medians and proportions and stratified by treatment group (moxa and no-moxa). Pearson and Fishers exact Chi-square test were used to test the association between categorical variables both before and after treatment. T-test and Kruskal-Wallis tests were respectively used to test for differences in mean and medians of numeric variables across the different levels of categorical variables.

3. Results

3.1. Recruitment and participant flow

All participants were recruited between January 2012 and January 2014. Each one initially attended clinic at the time of randomisation (baseline) and then at designated intervals for the following 6 months (Diagram 1).

3.2. Losses and exclusions

By the end of month 2 (a primary way marker for sputum conversion) 14 patients had either been lost (died, self- referred to another centre or lost to follow up) or excluded from the study. By the end of month 6 a total of 36 had been lost (including either failed treatment or excluded as confirmed MDR-TB).

These changes meant that the number of patients compared in each analysis depend upon the stage of the study. Accordingly, N values are stated in each Tables 2–9.

3.3. Baseline data

Details of the baseline characteristics are shown in Table 1. Based on these characteristics there were no statistical differences between the two treatment groups.

3.4. Outcomes and estimations

3.4.1. Karnofsky score

The median average at enrolment was scored at 70%. There was an almost universal improvement of more than 20 in both groups with no significant differences so no data is reported.

3.4.2. Effect of adjunctive moxibustion on sputum conversion rate (all patients)

Table 2 shows sputum conversion among all 180 patients on first-line TB treatment, with and without moxa.

In the first month of treatment, 10 patients using moxa and only 2 patients in the control arm had converted to sputum negative, showing a statistically significant difference among the two arms ($p = 0.032$).

After 2 months of treatment, most patients (83.9%) had converted to negative. The conversion rate was slightly higher, however, (87.8%) for the cohort using moxa compared with the control treatment (79%) although this difference was not statistically significant.

3.4.3. Changes in CD4 count (all patients)

Table 3 shows the CD4 values for all 180 patients on first-line TB treatment, with and without moxa.

Both groups saw improved CD4 counts with no statistically significant effects although the changes in the moxa group were larger at 6 months with the median values of differences between the two groups – 273 vs 151–showing an 80% difference.

3.4.4. Haemoglobin levels (all patients)

At baseline all the median levels of haemoglobin were borderline

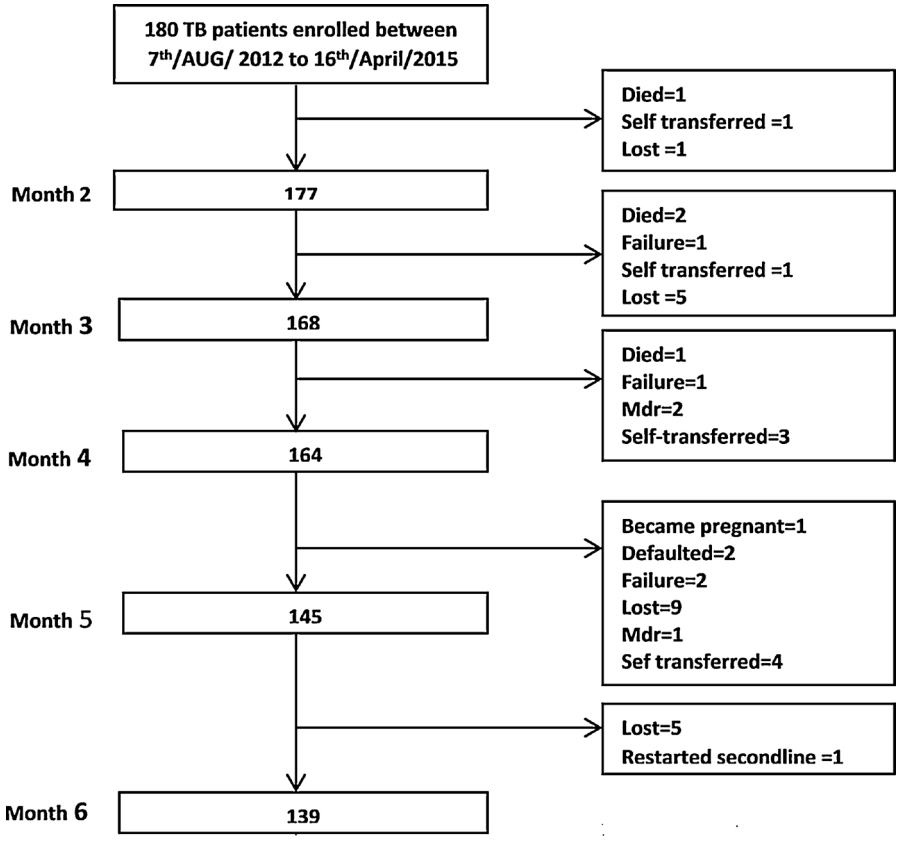

Diagram 1. Study Participant flow.

Table 1
Baseline Characteristics of patients included in both study arms. N values shown indicate numbers of patients. (Comparisons were made using Pearson and *Fishers exact chi-square test statistic and Wilcoxon rank sum test of medians).

Baseline characteristics	Overall	Randomization		p-value
	N = 180	No Moxa n = 90	Moxa n = 90	
Gender-n (%)				0.356
Male	112(62.2)	59(65.6)	53(58.9)	
Female	68(37.8)	31(34.4)	37(41.1)	
Age in complete years–n (%)				0.297
15–30	103(57.2)	56(62.2)	47(52.2)	
31–45	64(35.6)	27(30.0)	37(41.1)	
Above 45 years	13(7.2)	7(7.8)	6(6.7)	
Body mass index-n (%)				0.102
Underweight	91(50.6)	40(44.4)	51(56.7)	
Normal	80(44.4)	43(47.8)	37(41.1)	
overweight	9(5.0)	7(7.8)	2(2.2)	
HIV sero status- n (%)				0.350
Positive	49(27.2)	24(26.7)	25(27.8)	
Negative	128(71.1)	63(70.0)	65(72.2)	
Not done/unknown	3(1.7)	3(3.3)	0(0.0)	
Weight in kgs-median(IQR)	51(46–57)	53(47–58)	50(46–57)	0.360
Karnofsky score-median(IQR)	70(70–80)	70(70–80)	70 (65–80)	0.220
Cd4- median(IQR)	519(330–740)	530(345–764)	518(318–709)	0.460
Haemoglobin – median(IQR)	12(9–13)	12(10–13)	10(9–13)	0.052

Table 2
Sputum conversion rates among patients in both study arms over 6 months of treatment. (Comparisons made using Pearson and Fisher's Exact chi-square exact test) totals showing numbers (and percentages in brackets).

Time(Months) hshhs)	Total nnumbernumbersOverall (%)	No Moxa	Moxa	p-value
1	12(6.7)	2(2.2)	10(11.1)	**0.032**
2	151(83.9)	72(80.0)	79(87.8)	0.156
3	164 (91.1)	79(87.8)	85(94.4)	0.202
4	166(92.2)	79(87.8)	87(96.7)	0.130
5	171(95.0)	82(91.1)	89(98.9)	0.120
6	172(95.6)	83(92.2)	89(98.9)	0.210

Table 3
Changes in CD4 levels among patients on first-line TB treatment with and without adjunctive moxibustion over 6 months treatment period. (All comparisons were made using the Wilcoxon rank sum test) N values shown are numbers.

(Cd4 count in cells/μL)	All	No Moxa	Moxa	p-value
Baseline CD4 – median (IQR) (range) N = 180	519 (330–740)	530 (345–764)	518 (318–709)	0.460
Cd4 count at 6 months – median (IQR) (range) N = 139	752 (520–991)	681 (541–904)	791 (474–1059)	0.56

Table 4
Haemoglobin levels among patients on first-line TB treatment with and without adjunctive moxibustion over 6 months treatment period. (All comparisons made using the Wilcoxon rank sum test) N values shown are numbers.

	All	No moxa	Moxa	p-value
Baseline Haemoglobin (ctHB g/L) – median(IQR) **(N = 180)**	12 (9–13)	12 (10–13)	10 (9–13)	0.052
Haemoglobin at 6 months (N = 139)	15 (14–16)	14 (14–15)	15 (14–16)	**0.003**

anaemic or below as defined by the WHO technical working group of a hemoglobin concentration of less than13 g/dl for men and less than 12 g/dl for females. [27] (See Table 4). After 6 months the median levels of both treatment groups had increased to healthy status, but with a significantly larger improvement in the moxa group. Comparing the medians of individual changes in haemoglobin over this period produced a significant effect of moxa (P = 0.03).

3.4.5. Adherence rates

Adherence was assessed on every clinic visit in line with standardised methods as practised at tuberculosis treatment centres in the Ugandan National TB Programme. Patients were asked whether they forgot to take their medicine, whether they were careless at taking their medicine, whether (when they felt better) they sometimes stopped taking their medication, or whether they felt worse and stopped taking their medication. If a patient declared none of these in any all their visits, then they were designated as having good adherence.

Results (See Table 5) indicated that adherence was statistically different across the treatment arms and that patients using moxa had improved adherence to treatment compared to those on the standard TB treatment (p = 0.001).

3.5. Ancillary analyses

On the basis that the effects of adjunctive moxa might differ in HIV positive cases, and knowing that co-infection is a hallmark of TB in Africa, we pre-specified a secondary subgroup analysis with respect to both sputum conversions and blood results of HIV positive patients. HIV status was not taken into account at all at randomisation and a total of 25 of the 90 no-moxa patients were HIV positive, compared with 24 of the 90 moxa patients.

3.5.1. Sputum conversion in HIV-positive cases

The median conversion rate for these patients was slower than for the whole study set shown in Table 2 although in the first month of treatment there was no difference between the two treatment groups (See Table 6). However after 2 months of treatment, 80% of moxa patients had converted to sputum negative as opposed to 54% in the control group although this was not statistically significant. Given the statistically significant difference that appeared in the moxa group compared with the no-moxa patients in the whole cohort (see Table 3) it seems possible that a similar moxa-provoked response might have appeared slightly later in these HIV+ patients. Although this did not show as being statistically significant the authors consider it to be worth reporting because the trends in both tables look similar. It should also be noted that at all times during the study the conversions remained higher in the moxa patients, though these differences were again not statistically significant.

Table 5
Adherence rates among the two study arms over 6 months of treatment. (Comparisons are made using Pearson and Fishers exact chi-square test statistic and Fishers exact test *p*-value) N values shown are numbers of patients with percentages of cohort in brackets.

	Overall (n = 178)	No Moxa (n = 89)	Moxa (n = 89)	p-value
Adherence n (%)				**0.001**
Good adherence	152(85.4)	68(76.4)	84(94.4)	
Poor adherence	26(14.6)	21(23.6)	5(5.6)	

Table 6
Effect of adjunctive moxibustion on sputum conversion rate among HIV-positive patients in the study. (Comparisons made using Pearson and Fisher's Exact chi-square exact test) N values shown are numbers of patients with percentages of cohort in brackets.

Time(Monthshs)	Overall n (%)	No Moxa(n = 24)	Moxa(n = 25)	p-value
1	2(4.1)	1(4)	1(4)	1.00
2	33(67.4)	13(54)	20(80)	0.07
3	41(83.7)	19(79)	22(88)	0.40
4	43(87.8)	19(79)	24(96) 24(96)	0.07
5	46(95.0)	21(87)	25(100)	0.11
6	47(95.9)	22(92)	25(100)	0.24

3.5.2. CD4+T cells in HIV positive cases

As expected, the CD4 baselines were much lower in these co-infected patients (Table 7).

The CD4 counts improved with treatment in both groups, with the median values of differences between the two groups – 263 vs 209–showing a 26% difference, but this difference was not statistically significant. Given the impact of HIV infection on the progression of tuberculosis, this is considered by the authors as still being worth reporting.

3.5.3. Haemoglobin levels in HIV positive cases

Similarly to 'all TB cases' at baseline the median levels in HIV positive cases were borderline anaemic or below (See Table 8). However, median baseline levels were significantly lower in moxa patients. After 6 months both groups had recovered to similar median values, with the rise in haemoglobin of the moxa group being significantly larger (P = 0.003).

3.6. Adverse effects of moxa

The proportion of patients experiencing any adverse event was similar between the two groups. (See Table 9).

It should furthermore be noted that there were no reports of harms specifically related to moxa applications (i.e. burns or blisters).

4. Discussion

4.1. Interpretation of results

Previous unpublished pilot studies by Moxafrica had provided

Table 7
CD4 counts among HIV positive patients in the two study arms. (All comparisons were made using the Wilcoxon rank sum test) N values shown are numbers.

(Cd4 count in cells/μL)	all	No Moxa	Moxa	p-value
Baseline CD4- median (IQR) Range **N = 49**	369 (230–653)	392 (238–667)	366 (230–587)	0.670
CD4 count at 6 months – median (range) **N = 25**	615 (397–811)	601 (495–763)	629 (301–823)	0.56

Table 8
Haemoglobin levels among HIV positive patients in the two study arms. (All comparisons made using the Wilcoxon rank sum test). N values shown are numbers.

	All	No Moxa	Moxa	p-value
Baseline Haemoglobin − (ctHB g/L) median(IQR) **N = 49**	10(9–13)	12(10–13)	10(8–12)	0.040
Haemoglobin at 6 months **N = 25**	15(14–16)	14(14–15)	15(14–16)	0.003

Table 9
Prevalence of adverse events among patients on first-line TB treatment with and without adjunctive moxibustion over the 8 months period of treatment N values shown are numbers with percentages in brackets.

Adverse events	Overall n(%)	Treatment		
		No Moxa	Moxa	p-value
Pulmonary				0.90
Absent	68(76.4)	19(76.0)	49(76.5)	
Present	21(23.6)	6(24.0)	15(23.4)	
Abdominal pain				0.20
Absent	85(95.5)	25(100.0)	60(93.8)	
Present	4(4.5)	0(0.0)	4(6.25)	
Neurologic problems				0.56
Absent	71(79.8)	19(76.0)	52(81.3)	
Present	18(20.2)	6(24.0)	12(18.7)	
Skin infections				0.18
Absent	75(84.3)	19(76.0)	56(87.5)	
Present	14(15.7)	6(24.0)	8(12.5)	
Cardiovascular problems				0.99
Absent	75(84.3)	21(84.0)	54(84.4)	
Present	14(15.7)	4(16.0)	10(15.6)	
Musculoskeletal problems				0.16
Absent	50(56.2)	17(68.0)	33(51.6)	
Present	39(43.8)	8(32.0)	31(48.4)	

anecdotal evidence of improved appetite and energy as well as a reduction in joint pains. However, monthly monitoring throughout this study did not reveal any evidence of such effects. At the same time, however, no adverse effects of moxa were reported, indicating that the treatment is safe as an adjunctive therapy for those taking both first-line TB drugs and Highly Active Anti-Retroviral Therapy (HAART).

The results of this study suggest that the use of adjunctive moxa enables a faster sputum conversion rate, allows greater recovery of haemoglobin levels and may lead to some increases in CD4. These would all be generally considered to be beneficial effects in TB patients' recoveries if they are confirmable in the future.

If this type of moxa therapy is indeed immunomodulatory (as is suggested by other previous research [22]) it is likely that some or all of these changes may have been elicited by a moxa-provoked host-directed immune response. If this was indeed the case, then (despite there being no direct evidence from this study) it is reasonable to further suggest that similar effects might be seen in all types of TB patients regardless of TB strain (i.e. particularly those patients who will be at most critical risk in the coming years from MDR-TB and XDR-TB, including those co-infected with HIV). Furthermore it can be suggested that such effects may also be dependent on dosage.

4.1.1. Drug-resistant TB

Tuberculosis mycobacteria vary globally in terms of genetic strains and these in turn confer varying degrees of virulence. Since the advent of TB drugs some of these strains have evolved even further to vary in terms of their respective capacities to resist the anti-TB drugs themselves (varying from resistance to a single anti-TB drug to strains that are resistant to all available anti-tuberculosis medication). If moxa were to be shown to support or promote recovery from these more dangerous strains (as well as from drug-susceptible strains as suggested by this study – strains which are normally curable) this could be of significant public health benefit. In this respect, the study's authors conceive of future similar small studies conducted in a variety of TB endemic countries as part of existing TB projects which are already specifically treating local epidemics of drug-resistant TB. This could be a highly efficient and economical way of eliciting more information of this therapy's potential value in a variety of environments with ethnically different patients infected with genetically different strains of disease. It would be of extraordinary value of the results were shown to generally improve either treatment outcome, treatment adherence or both. The authors also suggest this therapy's potential as a palliative tool for supporting patients who have failed all therapy (who frequently have little or no care at all and remain infectious with lethal strains of disease up until their death) and suggest urgent investigation in this situation as well given the paucity of care available for such patients and their precarious epidemiological status.

Given the relatively high success rates (83%) of treating drug-susceptible TB [2], it can only be suggested that there would only be a modest public health pay-off if moxa was used as part of standard care. However, with the much lower reported success rates of MDR- and XDR-TB (54% and 30% respectively) [2] the use of moxa could provide a proportionately far more significant therapeutic advantage if similar effects were to be seen in these patients – or indeed if a larger effect could be elicited with a larger moxa dosage.

4.1.2. Dosage

It is important to note that the moxa dosage was deliberately minimised in this study so that the patients could self-administer their treatment (added dosage would have necessitated administration of the moxa by a helper since the extra treatment points would have been on the back). This choice was made based on anecdotal evidence from the unpublished pilot studies (that moxa only on the two leg points would be enough to see measurable differences emerge in drug-susceptible cases treated with first line TB drugs). It was reasonably assumed that this would maximise completion rates and therefore produce more rigorous results. It is quite possible, therefore, that increased moxa dosage could provoke a stronger immune response.

These current findings could be of particular relevance because moxa has been found to be safe, and is so cheap and potentially sustainable. Furthermore (because it is inherently a low-tech intervention) it is highly adaptable for even the most resource-poor or remote point-of-care environments. This latter issue is a challenge even for first line drug treatment of TB but is of a different order entirely for DR-TB. The most regularly identified problems with existing second-line treatments for DR-TB are that they are too expensive, too lengthy, have limited treatment success rates, are extremely challenging to manage (even in middle-income countries where so much of the burden of MDR-TB is believed to exist), and/or are too toxic for the patient to tolerate [28]. The emerging findings point to the possibility that moxa might be shown to mitigate one or more of these problems and (if so) should do so without the risk of stoking further drug-resistances in the mycobacterium in the process.

Table 10 suggests the possible add-on costs of moxa in the context of the existing regimens, their costs and their relative success rates. The costs in the moxa row include material for a higher dosed regimen.

4.1.3. HIV co-infection

HIV-positive anaemic TB patients, especially those with low CD4 cell counts, have been shown elsewhere to have poor recovery during TB treatment, though studies have also confirmed the ability of HAART to correct or improve the anaemia alongside the other haematological parameters of HIV infection [29].

When HIV + patients were examined as a separate sub-group in this study, there were some indications that beneficial effects of moxa might

Table 10
A comparison of treatment complexities between different types of Tuberculosis.

	Drug-susceptible TB	MDR-TB	XDR-TB
Resistance to:	n/a	2 drugs	4 + drugs
Total treatment time	6–8 months	24 month	24 + months
Intensive phase	2 months (4 drugs)	8 months (5–6 drugs)	12 months (5–6 drugs)
Continuation phase	4–6 months (2 drugs)	12? months (4 drugs)	18? + months (4–6 drugs)
Success rate	83%	52%	28%
median cost[i]	$1253[i]	$9529[i]	$2000–200,000
Adjunctive moxa cost	< $10	c. $30–40	c. $30–40

[i] WHO. Global Tuberculosis Report 2017. Geneva, Switzerland: World Health Organization, p, 107.

be greater than in the study group as a whole although this turned out to be a smaller sub-group than anticipated because of disproportionate drop out between months 2 and 6 in this group. These indications included suggestions of a more rapid sputum conversion rate after 2 months (with the sputum conversion data appearing not to have been affected by the disproportionate drop-out), an improved rate of haemoglobin reconstitution that was statistically significant (P = 0.03) and a possible greater increase in CD4 compared with control group. While this effect on CD4 was not statistically significant it still suggests an interesting potential considering the devastating effect that the HIV pandemic has on the prognosis of TB.

All HIV positive cases were also on anti-retroviral medication, and as a consequence the data further tentatively suggest the possibility that moxa may help improve the effects of the anti-retroviral ARV drugs while at the same time supporting the TB drugs.

4.2. Limitations

Blinding of the patient had been initially considered to increase scientific rigour (i.e. to add a third 'sham' arm) but, because of the nature of the intervention itself and the uncertainty of its mechanism of action, it was concluded that it was effectively impossible to add a placebo which would involve use of heat if any of the effects were thermoceptive.

There were unavoidable limitations in the study design relating to the blinding of the doctor and the non-blinding of the study nurse. In the case of the doctor there were inevitable possibilities that a patient would reveal which arm of the study he/she was on during interview. With regard to the senior study nurse, there were possibilities that her usual management of the intervention patients might have been biased given that she knew which arm of the study they were on. Generally constant efforts were made to minimise the risks that this limitation might have had on the final data. It can have little or no impact on the serological and sputal outcome data (which forms the bulk of the report) of course, although we recognise that it is possible that it could have had an effect on the adherence data about which there was also statistically significant data.

A loss-to-follow-up rate of 5% had been originally estimated which transpired to be an under-estimation (in the event the total loss-to-follow up at 6 months was 23% which had obvious impact on much of the data). It should be noted, however, that the key data on sputum conversion all fell within the 5% that had been estimated at outset.

The authors furthermore accept that much of the discussion section (specifically relating to the potentials of using moxa for supporting treatment of MDR-TB) is not substantiated directly by the data presented. Given the scale of the public health threat from MDR-TB and the lack of effective response, however, this limitation was unavoidable: it would have been both unreasonable and unethical to conduct an RCT looking at responses of MDR cases at first instance; however with the benefit of the data from this study relating to drug-susceptible disease it seems quite reasonable to use these as corroborative evidence for making a case for further research looking at MDR or XDR disease.

The authors furthermore recognise that the low 'N' values for HIV cases in the Hb and CD4 tables (see Tables 7 and 8) only emerged at the final review of the data and it was realised immediately that these numbers were unexpectedly low. This was, of course, not one of the planned primary outcomes anyway but nevertheless it still is, in the opinion of the authors (despite the low numbers), important to report.

Dosage issues: as discussed previously, the protocol was deliberately set so that it would require self-administration of the moxa therapy (and therefore maximise treatment adherence by the TB patients and therefore enable more robust statistical outcomes). This made for an obvious limitation of the study in that the dosage of moxa stimulation was deliberately set relatively low: were it to have been increased it could possibly have made for more significant data outcomes but could also have resulted in higher drop-out rates.

Finally during the course of the study GeneXpert was added to the onsite laboratory facility; GeneXpert is a more specific and sensitive bacteriological test for TB than sputum microscopy and can also diagnose Rifampicin resistance. It would have possibly improved the resulting data if it had been included as the base diagnosis. It was not added to the diagnostic algorithm of the study design, however, because it had not been available for all enrolled patients (although it was used once it was available to confirm Rifampicin resistance and therefore exclude some cases from the study).

Registration

The trial is registered at the Pan African Trials Registry no: PACTR201504001033387.

Protocol

Full details of the trial protocol can be found on the moxafrica website. https://www.moxafrica.org/copy-of-uganda-project-1.

Funding

This study was funded by Moxafrica (UK based charity no. 1128408). Moxafrica was involved in the design of the study and provided logistical support during the trial but were not involved in the preparation of the statistical analysis plan. The analyses themselves were performed by the University of Makerere's School of Health Sciences. The manuscript was prepared by the authors led by Professor Paul Waako. Moxafrica was permitted to review the manuscript and suggest changes, but the final decision on content was exclusively retained by the authors.

Conflicts of interests

There were no conflicts of or competing interests.

Acknowledgements

The authors thank the efforts and dedication of Rehema Kigongo, Dorothy Nabuule and Denis Kayanja at Kiswa Health Centre for helping to see this study completed. The authors also acknowledge the support of the North American Journal of Oriental Medicine which donated the moxa floss that was used in the study.

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