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Original article

Single dosage of doxycycline for prophylaxis against leptospiral infection and leptospirosis during urban flooding in southern Thailand: A non-randomized controlled trial

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ABSTRACT

This study was conducted to investigate the protective efficacy of a single dosage of 200 mg doxycycline against leptospiral infection and leptospirosis and associated risk factors among residents exposed to flooding in southern Thailand. Of 641 participants, 600 received doxycycline while 41 did not. Twenty two participants were infected with *Leptospira* and six developed leptospirosis. Having a laceration wound was significantly associated with leptospiral infection (odds ratio [OR] = 37.20; $P < 0.001$) and leptospirosis (OR = 18.24; $P = 0.003$) whereas exposure to flood more than 3 h per day was associated with only leptospiral infection (OR = 3.70; $P = 0.038$). Seventeen participants who received doxycycline and five who did not, were infected with *Leptospira*, resulting a protective efficacy of 76.8% (95% confidence interval [CI] = 34.3%–92.0%). Four who received doxycycline and two who did not, developed leptospirosis, resulting a protective efficacy of 86.3% (CI = −9.8%–98.2%). Among the participants with laceration wound, the protective efficacy for leptospiral infection was 92.0% (CI = 81.2%–96.6%) and for leptospirosis was 95.6% (CI = 78.2%–99.3%). Among the participants exposed to flood water less than or equal to 3 h per day, the protective efficacy for leptospiral infection was 89.2% (95% CI 63.6%–96.67%). A single dosage of 200 mg doxycycline for prophylaxis might be effective for preventing leptospirosis among flood victims with laceration wound after recent flood exposure.

1. Introduction

Leptospirosis, a bacterial zoonotic disease, is emerging and re-emerging as an important public health problem in many countries [1]. The disease is caused by spirochetes belonging to the genus *Leptospira* which can exist in diverse environments [2,3]. Climatic changes which increase humidity, raise the water table, or elevate subsurface water, often precipitates outbreaks in endemic areas and occasionally in non-endemic areas [3–8]. Although the majority of infected people have subclinical or self-limiting illnesses, among patients with severe forms of the disease, the case fatality rate is high, even after treatment with appropriate antibiotics [2,3]. Severe forms of leptospirosis are usually found during outbreaks because of under-diagnosis and also due to the association with acquisition of *Leptospira* in urban areas [9–11]. Several hypotheses have been proposed for explaining this phenomenon. Firstly, the concentration of causative *Leptospira* in urban areas is higher than in rural areas. Secondly, urban residents have a higher frequency of exposure to *Leptospira* than rural residents. Thirdly, the serovars of *Leptospira* in urban areas have severe pathogenesis themselves [10–12].

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Chemoprophylaxis is more practical and universal than other disease control strategies such as vaccination, elimination of animal reservoirs and usage of protective equipment because the *Leptospira* serovars, environments and human behaviors involving each outbreak vary [1–3]. Doxycycline, an antibiotic with efficacy against universal *Leptospira*, is widely recommended for treatment of leptospirosis whereas data of prophylactic efficacy against this infection is limited [13–15]. Although several clinical trials have been conducted to evaluate the protective efficacy of doxycycline against leptospirosis, none of them were conducted during periods of flooding [16–18]. A study from Guyana found that the regime can limit the number of cases after an outbreak and studies from the United States and Barbados found it to be cost-effective during both high and low-incidence periods [19,20].

On September 28, 2010 unusually heavy rainfall in Hat Yai City of southern Thailand led to extensive and rapid flooding. On October 3 the water level in the municipality area peaked at 3 m, rapidly decreased on October 5 and completely receded on October 10. Here we conducted a study to evaluate the protective efficacy of single dosage doxycycline against leptospiral infection and leptospirosis and to determine associated risk factors for this disease.

2. Materials and methods

2.1. Ethics statement

This study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Prince of Songkla University (EC: 54-080-14-1-2) and was registered with the Thai Clinical Trial Registry (TCTR) subsequent to the enrollment process. The identification number is TCTR20131106001. All those approached had an opportunity to refuse to join the study or, after agreeing to join, withdraw at any time. Written consent was obtained from all enrolled participants prior to initiation of data collection and intervention. All participants and non-participants were given the standard basic medical care and advice. The data collection form was independent of the hospital medical records and participants could only be identified via their unique identification number. The identity of the participants was kept separately from the data collection form. Data collection forms, consent forms and identity of each participant were kept sealed and opened only by authorized researchers.

2.2. Study setting

Hat Yai City is located at 7°1′N 100°28′E in the southern Thailand near the northern border of Malaysia. The city has a population of approximately 300,000 and covers approximately 8.0 square miles. The majority of this area is dominated by governmental administration offices, businesses, shopping centers and residences. Hat Yai City has a tropical climate with only two seasons; rainy and dry. The rainy season occurs from May to December and is influenced by southwestern monsoons. Occasional floods occur during October to November.

Hat Yai City is an endemic area of leptospirosis with a reported incidence rate of 0.86–5.50 cases per 100,000 population per year during 2000–2009. After severe flooding in November 2000 and December 2005, the incidence rate in those two months increased to 20 and 18 cases per 100,000 population, respectively, an increase of 10 and 15 times the average incidence per year (2.0 cases and 1.2 cases per 100,000 population per year in 2000 and 2005, respectively).

2.3. Study subjects

All residents who lived in Hat Yai City, aged 18 years or above and were exposed to flood water since October 3, 2010 were eligible to be enrolled in this study. Pregnant women, lactating mothers and those who felt sick or took any antibiotics on the day of enrollment were excluded.

2.4. Conduct of study and intervention

The study was conducted between October 8 and October 10, 2010. A randomized or placebo controlled trial was not possible because the study was conducted as a part of the rapid response service of Songklanagarind Hospital and registered to the TCTR subsequent to the enrollment process. Five physicians were responsible for interviewing the participants and conducting physical examinations. Five researchers were responsible for recording the data with supervision from the physicians. The purpose of the study was explained to the enrolled participants, in particular the efficacy of doxycycline for prophylaxis against leptospirosis as well as the limitations, possible adverse drug reactions and contraindications. The participants were encouraged to feel free to join the study with or without taking doxycycline. After obtaining written consent, the participants were interviewed and examined by the physician while the researchers concurrently recorded the patient data.

Variables recorded included age, sex, underlying diseases, medical co-administration and previously reported risk factors such as working in a high risk occupation, lacking appropriate body protection against flood water, such as rubber boots, and exposure to rodents during the flood [5–8]. High risk occupations included scavengers and freshwater fishermen. The length of flood exposure was determined from the first date of exposure till the date of first assessment. Duration of exposure per day was determined by the average hours of flood exposure per day. Physical examination included general examination and characteristic of skin disruptions. Abrasion wound was defined as a wound caused by superficial damage to the skin, that is, not deeper than the epidermis. Laceration wound was defined as a wound caused by tearing of the skin deeper than the epidermis and through the soft tissue. Puncture wound was defined as a wound caused by an object penetrating through the skin. Avulsion wound was defined as a wound where the skin and soft tissue was partially ripped from the body. 5-mL blood specimens were obtained from the participants for serological testing. We offered two tablets of 100 mg doxycycline to participants without any contraindication and to those who agreed to take the medication. We encouraged participants to drink at least 500 mL bottled water and stay in an upright position for at least 2 h after taking doxycycline. The participants were observed 2 h after taking doxycycline for observation of adverse drug reactions.

All participants were scheduled for a second assessment 2–3 weeks later (October 22 to November 5, 2010) or earlier if they became ill or developed an adverse drug reaction. The second assessment included interview, physical examination and collection of a second 5 mL blood specimen for serological testing. Variables recorded included symptoms of illness, adverse drug reactions, flood exposure after first assessment, and medication taken including antibiotic co-administration during follow up. Participants who returned earlier than scheduled, due to illness or otherwise, had their data collected immediately.

2.5. Outcomes of the study

2.5.1. Primary outcome

We established the presence of leptospiral infection (seroconversion) on the basis of a fourfold or greater increase in indirect immunofluorescent antibody test (IFAT) for specific leptospiral IgG and confirmed with a fourfold or greater increase in leptospiral agglutination titer with a microcapsule agglutination test (MCAT)

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