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Lippia alba (Mill.) N. E. Brown hydroethanolic extract of the leaves is effective in the treatment of migraine in women

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ABSTRACT

Background: There is no universally accepted and effective prophylaxis of migraine headache episodes. We aimed to investigate the effects of *Lippia alba* (Mill.) N. E. Brown (chemotype geranial-carvenone) in the treatment of migraine patients.
Methods: Twenty-one women were enrolled in a prospective, phase 2, non-controlled cohort study to orally receive hydroethanolic extract of *L. alba* leaves. Symptom intensity and impact were assessed using MIDAS and HIT-6 instruments before and after 2 months of treatment.
Results: We observed a significant decrease on HIT-6 total score, as well as MIDAS number of missed days, number of headache days, and pain intensity. More than 70% of patients experienced a minimum 50% reduction on pain frequency.
Conclusions: Treatment with *L. alba* leaves (geranial-carvenone) hydroethanolic extract is a cheap, safe, widely available, highly effective therapy to reduce both the intensity and the frequency of headache episodes of women with migraine.
ClinicalTrials.gov Identifier: NCT01259947.

Introduction

Migraine is a common neurovascular disease characterized by headache and hypersensitivity to normal afferent stimuli, like light, sound and head movements, as well as autonomic symptoms (Ferrari 1998; Goadsby and Sprenger 2010). It is a disabiliting condition present in about 20% of people worldwide (1 male for 3 females) (Ferrari 1998). However, its pathophysiology is still unclear. Drugs most commonly used for migraine prophylaxis include beta-blockers, anticonvulsivants, calcium channel blockers, antidepressants, serotonin antagonists and nutraceutics. However, results of those treatments are variable and not universally accepted. In addition, medication overuse can worsen the pain episodes. Therefore, the development of new treatments for migraine is highly desirable (D'Amico 2010; Edvinsson and Linde 2010; Garza and Schwedt 2010).

The use of herbal medicines has been previously reported for the treatment of migraine (Antonaci et al. 2010; D'Amico 2010; Edvinsson and Linde 2010; Ferrari 1998; Garza and Schwedt 2010; Goadsby and Sprenger 2010), but they lack scientific evidence of efficacy.

Lippia alba (Mill.) N. E. Brown (Verbenaceae; "cidreira") is an herb native from South America. Its main medicinal properties are analgesic, anti-inflammatory, anticonvulsivant and myorelaxant (Aguiar 2006; Aguilar 1988; Costa et al. 1989; Boorhem et al. 1999; Hennebelle et al. 2008; Mors et al. 2000; Saad et al. 2009). Its use as medicine is approved in Brazil (Brasil 2010), and its general safety is well known (Aguiar 2006; Carballo 1994; Fun and Svendsen 1990; Saad et al. 2009).

We have previously shown that the hydroethanolic extract of the leaves of a particular chemotype of *L. alba* (geranial-carvenone) is highly effective in reducing both the intensity and the frequency of headache episodes of patients with migraine (Conde et al. 2011). However, in that study, loss-of-follow-up was high, almost only women were studied, the data were retrospectively collected, and data collection instruments were not validated. In this study, we aimed to prospectively evaluate the therapeutic effect of the

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hydroethanolic extract of *L. alba* leaves (geranial-carvenone) in women with migraine using validated instruments.

Materials and methods

Study design

We conducted a longitudinal, prospective, phase 2, non-controlled cohort study. The study was conducted according to the principles of the Declaration of Helsinki and Tokyo and approved by our institutional review board (process #14786/2010). A signed informed consent was required. The study was registered in ClinicalTrials.gov (NCT01259947). To demonstrate a 5 points reduction in the HIT-6 total score (SD of 7.5 points), $\alpha = 0.05$ and $1 - \beta = 0.8$, in a paired analysis, minimum sample size would be 20 patients.

Sampling

Patients with a clinical diagnosis of migraine, with or without aura, were recruited from the Ambulatory of Herbal Medicine of the Spiritist Society "Terra de Ismael" (Jardinópolis, SP, Brazil). Migraine diagnosis was made in a clinical basis according to internationally accepted criteria (ICHD-II 2004; Silberstein et al. 1996). Inclusion criteria were a diagnosis of migraine and age >18 years. Exclusion criteria were type-2 diabetes mellitus, headache from other causes, alcohol addiction, benzodiazepines or anticonvulsivants use, psychiatric disorders, or patient request.

Lippia alba hydroethanolic extract preparation

L. alba leaves were collected at Reserva Ecocerrado Brasil (Lat. 19°36′48,9″, Long. 47°08′20,8″, 929 m altitude), where it is cultivated under Brazilian government authorization. A voucher of *L. alba* species was deposited at the herbarium of the Biotechnology Department Ribeirao Preto University, with the reference number HPM 1213. The leaves were collected at 9 am, weighted and washed in water. Excess water was removed on filter paper sheets for 2 h. The leaves were submitted to quality control according to Brazilian regulations (Brasil 2010; Carvalho and Silveira 2010). Leaves (200 g) were then added to 1 l of 70% ethanol (water solution, v/v) and left to macerate for 10 days. After this, the extract was filtered using filter paper, resulting in tincture. The chemical composition is reported in Phytomedicine (Conde et al. 2011).

Treatment protocol

All patients received an initial oral dose of 1 drop of tincture per kilogram of body weight per day, twice a day. They were reassessed 60 days after treatment start. Current therapy was not discontinued. Headache episodes were controlled with analgesics or NSAIDs, per patient choice. The clinician prescribing the treatment was trained in internal medicine and herbal medicine; was licensed in São Paulo, Brazil; and had been practicing medicine for an average 14 years.

Clinical data collection

Clinical data were recorded on individual sheets. The migraine severity and impact were prospectively assessed by two different instruments: the Migraine Disability Assessment Scale (MIDAS) (Stewart et al. 1999), and the Headache Impact Test (HIT-6) (Kosinski et al. 2001).

Table 1
Demographic data ($n = 21$).

Age (years)	37.6 ± 10.8
Ethnicity (white)	20 (95%)
Body weight (kg)	63.9 ± 11.9
Body mass index (BMI, kg/m^2)	24.6 ± 3.9
Age of disease onset (years)	18.3 ± 9.6
Aura present	13 (62%)

Statistical analysis

The primary outcome was the HIT-6 total score after treatment. Secondary outcomes were days missed, pain frequency and intensity (MIDAS). Categorical variables were expressed as frequencies or proportions, while continuous variables were expressed as mean (±SD) or median (range), according to data distribution. The results after treatment were compared to baseline using a two-tailed Wilcoxon's signed rank tests. We used GraphPad Prism® 5.0 (La Jolla, CA, USA) software. We accepted a type I error level at $\alpha = 0.05$ by convention.

Results

Study population

From July 2010 to June 2012, 21 women were enrolled. There was no loss-of-follow-up. Demographic and baseline data are shown in Table 1.

Treatment effectiveness

Median initial HIT-6 total score was 64 (54–71), and decreased to 59 (36–69) after 2 months of treatment ($p < 0.001$, Fig. 1). The median initial number of missed days (MIDAS) was 19 (2–90) days, and decreased to 5 (0–13) days after treatment ($p < 0.001$, Fig. 2A). The median initial number of headache days (MIDAS) was 20 (3–90) episodes, and decreased to 5 (1–90) episodes ($p < 0.001$, Fig. 2B). The median initial pain intensity (MIDAS) was 7 (4–10), and decreased to 6 (1–10) ($p = 0.03$, Fig. 2C). No side effects were reported.

Discussion

We showed that the hydroethanolic extract of this particular chemotype of *L. alba* (geranial-carvenone) leaves is effective in

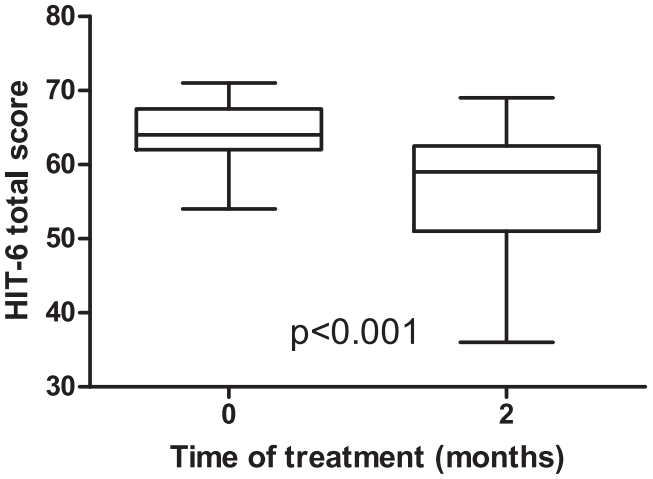

Fig. 1. Headache Impact Test (HIT-6) total score before and after treatment. The central line is the median, the boxes are interquartile ranges, and the bars are total ranges.