Study Protocol and Statistical Analysis Plan

Treatment of Chronic Itch in Patients Under Arsenic Exposure With Sublingual Naloxone: A Double-blind Randomized Controlled Trial

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Study design

To test whether the inhibition of β-endorphin (μ-opioid) receptor alleviates itch in patients under chronic arsenic exposure, we conducted a randomized, double-blind, placebo-controlled trial. We randomly assigned patients to naloxone (0.4 mg/qd, sublingual) and placebo (0.4 mg/qd, sublingual) using a computer-generated sequence of random numbers during January 2019 to March 2019. The trial consisted of a one-week treatment period and a one-week withdrawl period. The primary outcome (severity of itch) was evaluated using the NRS through a face-to-face interview on baseline (Day 0) and the last day of the treatment period (Day 7), and a telephone interview on the last day of the withdrawl period (Day 14). The participants were also inquired about the possible adverse events of naloxone such as headache, sleep difficulty, sickness, and dizziness in each interview.

Inclusion and exclusion criteria

The inclusion criteria include: the participants must be above 18 years, be able to understand the study protocol and sign informed consent voluntarily, and report moderate-to-severe itch (NRS≥3). Participants were excluded if they used anti-histamines, anti- inflammatory, anti-pruritic, analgesic, antidepressant, or anti-epileptic agents within 2 weeks prior to the study, or had a history of pruritic skin diseases such as eczema and psoriasis.

Statistical analysis

In the randomized controlled trial, an intention-to-treat (ITT) analysis was performed to evaluate the efficacy of naloxone. The last observation carry-forward (LOCF) imputation method was used for unmeasured data in drop-out participants. Mixed effect models were used to estimate the efficacy, by constructing a model: $Y = \beta_0 + \beta_1 Group + \beta_2 Time + \beta_3 (Group \times Time) + ei + \upsilon ij$, where β_3 is the estimate for efficacy; e_i and υ_{ij} refer to the errors between individuals and within an individual (repeated measurements), respectively. Statistical analyses were performed in R Statistical Software 3.4.1. The significance level for all statistical tests was 0.05.