ID: 2018ZY008-CTN

Research name:

Electroacupuncture Therapy for Change of Pain in Classical Trigeminal Neuralgia

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Study Protocol

Part1. Study objectives

1. To observe the therapeutic effect and safety of electroacupuncture (EA) in the treatment of classical trigeminal neuralgia (CTN).

2. To evaluate whether EA has the advantage over carbamazepine in the immediate effect, long-term effect and post effect of the analgesia in CTN.

3. To demonstrate whether EA has a synergistic effect with carbamazepine on the treatment of CTN, or even whether EA has an alternative effect on carbamazepine.

4. To establish a standardized, effective and convenient therapy program of EA to promote it widely.

Part2. Study program

1. Study subjects

1.1 Source of cases

It is expected that during the four years from January 2018 to December 2021, 120 patients with CTN will be recruited in the Third Affiliated Hospital of Zhejiang Chinese Medical University and Jiaxing TCM Hospital.

1.2 Diagnostic criteria

The diagnostic criteria are followed by *The international classification of headache disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629–808*, which was published by the headache classification committee of the International Headache Society (IHS)in 2013.

1) Pain of one side face should be conformed to the following criteria 2 and 3, with a paroxysm of at least 3 times.

2) Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution.

3) Characteristics of pain contain at least 3 of the following 4 characteristics:

A. Recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes.

B. Severe intensity.

C. Electric shock-like, shooting, stabbing in quality.

D. Precipitated by innocuous stimuli to the affected side of the face.

4) No neurological impairment.

5) Eliminating other disease that would cause the pain.

1.3 Inclusion criteria

1) Paroxysm pain involving branches of the 2nd and/or 3rd branch of trigeminal nerve.

2) The visual analogue score(VAS) baseline score ≥5 points, have a attack more than 3 times a day, at least 4 days a week.

3)18 years ≤ age ≤ 80 years.

4) Clear consciousness, have the ability of pain perception and resolution, can complete the basic communication.

5) Signed informed consent and volunteered to participate in this study.

1.4 Exclusion criteria

1) Those patients with epilepsy, head injury or other related neurological diseases.

2) Patients with serious heart, liver, kidney damage or cognitive impairment, aphasia, mental disorders, or unable to cooperate with the treatment.

3) Combined with hypertension but poor control.

4) Severe depressive with definitive diagnosis recently.

5) Pregnant and lactating patients.

6) Installing pacemakers.

7) For any other reason that is not suitable for the treatment of EA.

1.5 Removed criteria

The subjects who have entered a group of research but who were met one of the following conditions should be removed:

1) Those who do not meet exactly with the inclusion and exclusion criteria of the trial.

2) There are obviously adverse reactions during the treatment.

3) The subjects are not treated according to the treatment plan of the group after they have entered.

The removed cases should indicate the reason and retained the original medical records. No participation of statistical analysis of efficacy, but those who have received at least one treatment can participate in analysis of adverse reaction.

1.6 Shedding criteria

Cases that have been entered but not completed the treatment program should be considered as falling off, Such as the following situations:

1) Patient withdraws or has been lost their visit.

2) The acupuncture treatment has not reached 80%.

3) In the treatment, there are serious adverse reactions or adverse events.

The shedding cases should explain the reasons. If the case has been recorded the baseline data, and received at least one time acupuncture treatment, the results of its final main outcome can be carried out for statistical analysis. The medical records should be retained, while the data should not be carried forward during the follow-up.

1.7 Termination criteria

1) A diagnostic physician at each center will assess the severity of the disease in the study. If the subjects showed the symptoms of facial pain that could not be alleviated by acupuncture (the VAS score>8 points), the physician will assess the seriousness and terminate the study.

2) During the study period, the subjects had serious adverse events such as severe infection, coma, shock, even death and so on, the main investigator should be reported immediately and the study should be terminated immediately.

1.8 Clinical ethics and clinical trial registration

The ethics of two hospitals were approved before the trial beginning, and the clinical trials should be registered.

2. Study methods

2.1 Sample size estimation

The glmpower process of SAS9.3 software is applied to estimate the sample size. According to the literature and the preliminary experiment, the mean values of the

VAS score of EA+Carbamazepine group, EA+Placebo group, sham EA+ Carbamazepine group, sham EA+Placebo group ware 5.23,4.45,5.50,0.00.The standard deviation was 1.6. Under the condition of α=0.05, the test efficiency 1-β=0.8, the four groups were allocated with the 1:1:1:1 proportion, the sample size of each group was calculated at least 24. Considering the existence of shedding and other factors, in the premise of guaranteeing the minimum sample size, the sample size was enlarged by 20%to 30 cases in one group, in total 120 cases for 4 groups. Because of the complexity of the sample calculation process of factorial design, the formula is not listed here.

2.2 Random grouping

The random grouping operation is carried out by using dynamic randomization method of Central stochastic system (network edition). The exactly operation was same as the study 1.

2.3 Blind design and implementation

For the study is the acupuncture treatment, the doctor have to contact the patient directly. It's hard to put blind into practice to doctors. However, the other participants, including patients, observation index recorders, and data statisticians will be implemented blind. They are not aware of the groups of the subjects. At the same time, the subjects will be evaluated by blinding effect.

In order to ensure the better implementation of the blind, the study will provide separate treatment as far as possible for each subject. The measure will do the greatest degree to avoid the discussion between subjects from different groups for the feelings and effects.

2.4 Therapeutic method

The acupuncture needles of the study will be unified with HuaTuo brand disposable acupuncture needles produced by Suzhou Medical Products Factory CO., LTD., and the specifications are φ0.18 × 25mm and φ0.25 × 40mm. The EA instrument is unified by the acupoint neural stimulator HuaTuo SDZ- || B, which was produced by SuZhou Medical Supplies Co., Ltd.

(1) EA + Carbamazepine group

1) Acupuncture acupoints

Local acupoints:

Main acupoints: The affected side of Si-bai(ST2), Xia-guan (ST7), Di-cang (ST4).

Adjunct acupoints: Quan-liao (SI18) for pain in the 2th branch, Jia-che (ST6) for pain in the 3rdbranch and A-shi-xue(Two acupoints will be selected from the second branch or the third one).

Distal acupoints: The two sides of He-gu(LI4) and Wai-guan(TE5).

2) The position of acupoints

According to the 2006 People's Republic of China National Standard (GB/T 12346-2006) *"Acupoints names and positioning",* the position of acupoints is direct as follows.

Si-bai (ST2): On the face, the infraorbital hole.

Xia-guan (ST7): In the face, between the center of the zygomatic arch and the middle of the mandible.

Di-cang (ST4): In the face, next to the corner of the mouth 0.4 cun.

Quan-liao (SI18)： In the face, the lower edge of the cheekbones, out corner of eyes straight.

Jia-che (ST6): In the face, a transverse finger (middle finger) above the anterior angle of the mandibular angle.

A-shi-xue: Two points will be selected from the different branches, respectively, between the Xia-guan and Si-bai (the 2th branch)， and between the Xia-guan and Di-cang (the 3rd branch).

He-gu (LI4): On the back of the hand, the midpoint of the radial side of the second metacarpal.

Wai-guan (TE5): In the posterior area of the forearm, the distal side of the carpal dorsal distal is 2 inches, and the midpoint of the ulna and the radius.

3) Manipulation

Needling operation: Subjects with supine position, general relaxation, routine

disinfection of the facial skin. The superficial acupuncture will be applied for local points. The tiny needles (0.18×25 mm) will be selected to stimulate the local points with shallow row needling according to the distribution of neuropathy branch of trigeminal neuralgia. The technique should be lightly, the depth should be within 5 mm. It is not required a sense of "Qi" and should not touch the trigger point (the trigger points are the pain sensitive places that light touch can trigger severe pain, such as tiff, cheek, nose and so on. The doctor should have a communication with the subject before needling to clear the position of the trigger, do not needle or touch it.) The He-gu (LI4) and Wai-guan (SJ5) points will be selected as the distal points stimulating with 0.25×40mm needle (20-30mm depth). After the subject has a sense of acid distention ("get Qi"), the reducing method of twirling and lifting-inserting will be applied 10 times. If the subject is feeling pain seriously, the distal acupoints can be needling firstly with reducing method sharply until the pain relief. Then it's turn to needling the local acupoints .

EA parameters： The Xia-guan (ST7) and Quan-liao (SL18) (or Xia-guan (ST7) and Jia-che (ST6)), He-gu (LI4) and Wai-guan (SJ5) acupoints will be received EA treatment by HuaTuo SDZ- II B acupoint neural stimulator. The EA parameter is a dilute wave with 2/100 Hz, the treatment time is 60 minutes and the current intensity is comfortable to subjects.

4) Oral carbamazepine

Carbamazepine tablets (Jiangsu Pengli Pharmaceutical CO., LTD., 0.1g*100 tablets) should be took orally, 0.1g each time, thrice daily.

5) Frequency, duration and time

Treatment will be performed 3 times per week, and 4 weeks of continuous interventions for a total of 12 times.

(2) EA + Placebo group

In this group, the selection, positioning and manipulation of acupoints, the frequency, duration and retaining needle time of treatment are same as EA + Carbamazepine group; placebo, that appearance and specifications are the same as

carbamazepine, are cooperated taken of dose 0.1g, thrice daily.

(3) Sham EA+ Carbamazepine group

Selection of points and locations: the non-meridional points which are means to the points beside 5-10mm of the real acupoints (avoid the trigger point) in the EA group will be selected and needled with more shallow acupuncture (the depth of needling is about 1-2mm).

The operation of shame EA: The HuaTuo SDZ- II B acupoint neural stimulator with damaged electrode wires will be selected to connect the points next to the Xia-guan(ST7) and Quan-liao (SI18) , He-gu (LI4) and Wai-guan(TE5). The frequency, intensity and retaining time will be same as EA group. The subjects can see the display screen and parameter settings of stimulator, however there is no electricity output in fact.

The dosage and frequency of oral carbamazepine tablets are same as above part.

(4) Sham EA+ Placebo group

The points selection, positioning and manipulation are same as Shame EA+ Carbamazepine group，placebo are cooperated taken of dose 0.1g, thrice daily.

2.5 Emergency treatment

It is forbidden that another analgesic therapies are applied at any time during the trial except the patients continue not pain relief, and seriously affect the daily work and life, can use emergency (add) carbamazepine tablets 0.2 g, once time a day, after a meal. The use date and time and dosage of emergency drugs or other analgesic measures must be recorded in time.

2.6 Therapeutic effects indexes

Subjects are required to write a verifiable diary card to record their pain symptoms in 24 hours every day. The diary includes the following items: (1) daily attack frequency (spontaneous and provoking pain frequency); (2) provoking factors; (3) average pain intensity(VAS) in the past 24 hours; (4) side effect in the past 24 hours (including side effect of drugs or acupuncture); (5) Is there another analgesia therapies have been adopt ? Please record it.

(1) Indexes of main outcome evaluation

1) Change from Baseline Intensity of Pain at 6 months (evaluation of the pain by VAS with 0-10 points).

2) Change from Baseline Brief introduction of 2-week pain.

Evaluation method: According to pain diary, we will take average data of 2 weeks before treatment (-2~0 week) as baseline, 2 weeks of treatment phase (1~2 week) as data of treatment phase I, 4 weeks of treatment phase (3~4 week) as data of treatment phase II. During the follow-up period, the pain diary card will be continued in the 2 weeks before 3 months (11~12 week)/6 months (23~24 week) after treatments.

(2) Indexes of secondary outcome evaluation

1) Brief Pain Inventory-Facial scale (BPI-Facial)

2) Patient Global Impression of Change (PGIC)

3) Short-Form McGill Pain Questionnaire

4) Short- Form 36 Questionnaire

(3) Research cycle and evaluation time points

The treatment periods of this research are 4 weeks, and the follow-up period is 6 months. The above indexes are observed at the time points of baseline (the same day with the grouping and treatment for the subject), treatment period I (the end of the 2nd week), treatment period II (the end of the 4th week), follow-up period I (3rd months after treatment) and follow-up period II (6th months after treatment). The main outcome indexes will be measured weekly (1th week to 4th weeks) during the treatment period.

(4) Safety evaluation and acupuncture expectation evaluation

The relevant safety indicators during the treatment period and during the follow-up period are recorded at any time on the subjects' adverse event records, which is recorded by the acupuncture physician.

1) Safety evaluation of electric needle**:**

The abnormal acupuncture should be record, including broken needle, left needle, fainting, unbearable acupuncture pain (VAS≥8 points), local hematoma, infection and abscess. And the symptoms, average degree and average duration of other discomfort

after acupuncture, which refers to the duration of acupuncture 1 hours and above, appear the needle pain, nausea, vomiting, palpitations, dizziness, headache, anorexia and insomnia and other symptoms. Each time the patient is diagnosed and treated, ask if any of the above situations occur. If so, record it immediately.

2) Adverse reaction of carbamazepine:

Blurred or diplopia vision, drowsiness, weakness, nausea, vomiting, mental and/or neurological abnormalities and others.

3) Acupuncture expectation evaluation:

The evaluation is divided to "would be (1 point), not to be (-1 point), not clear (0 point)" to answer the curative effect of acupuncture treatment of CTN and other diseases. Time points: before acupuncture treatment, after acupuncture treatment, follow-up period.

(5) The evaluation of blindness

The subjects will be asked to accept true acupuncture, sham acupuncture or uncertainty. Researchers will compare the percentages of the two groups.

Evaluation time: at the end of the 4th week of any acupuncture treatment.

2.7 Quality control and quality assurance

The operators of the centers for specific acupuncture treatment must have the qualifications of the acupuncturist and are independent of the clinical treatment for more than 2 years. In order to ensure the smooth progress of the research, the first month before the clinical trial is officially launched, the research team will convene and complete the special clinical training, and conduct unified training for the clinical researchers of the two centers. Key train is carried out on that implementation of the subject and the Standard Operation Procedure (SOP) and gauge evaluation so that each clinical researcher is familiar with the research process and detailed implementation rules to improve the internal observation consistency of the researcher and the consistency between the observers, to ensure the reliability of the clinical study conclusion.

All observations and findings in clinical studies should be verified and confirmed repeatedly to ensure the reliability and authenticity of the data and to ensure that the

results and conclusions of clinical research are derived from the original data.

The applyment of specialized personnel for experimental data collection and statistics will control the test bias.

The quality control measures of each center. Regular monitoring of the two centers will be used to control the center-to-center bias.

2.8 Measures to improve the compliance of subjects

The compliance of patients was measured by the number of treatments. The calculation formula is as follows:

Criteria are the number of treatments that the subject has received over 80 percent of the treatment (including 80%).

In order to obtain a better compliance and make the final summation of the patient is not less than 80% of the total number of cases in the trial, so the following measures are adopted to improve patient compliance: Adhere to the principle of voluntary, sign the patient informed consent; We will improve and maintain the patient's compliance with the medical quality, the medical treatment environment, the medical expenses, etc., and encourage patients to persist in treatment during the study period; Provide the patient with a certain amount of transportation expenses and labor costs; Pay attention to the establishment of a good doctor-patient relationship, explain the purpose and necessity of the examination, treatment and review to the included cases, and obtain the consent and cooperation of the patients . Record the patient's contact information in detail for follow-up.

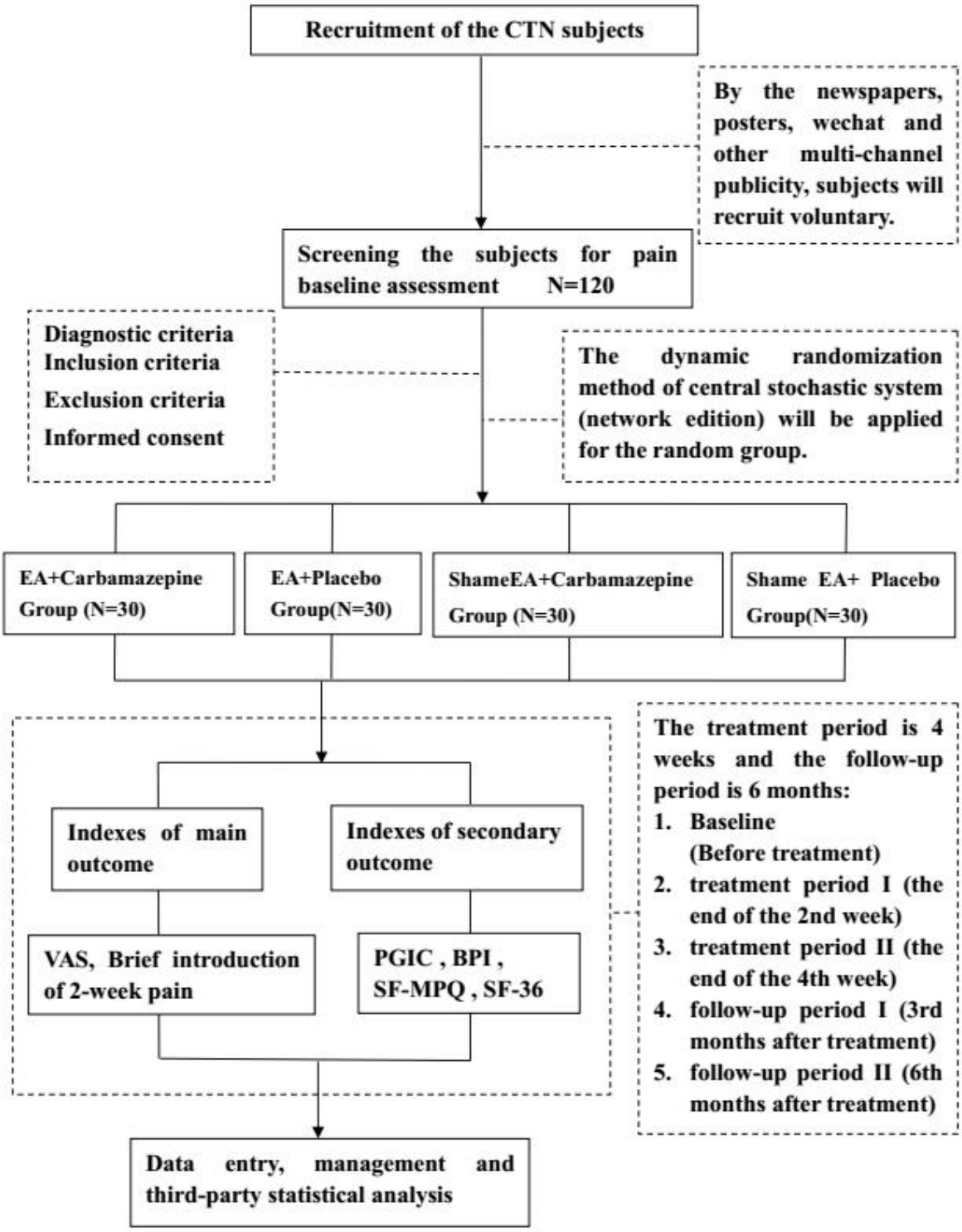
Part3. The key technology

1. The establishment of an effective treatment program of EA therapy for CTN is the first key technology in the study. The therapy technologies including acupoints selection, needing technique, EA parameters selection, needle retaining time, treatment frequency and how to apply acupuncture combined with carbamazepine.

2. The study design and the quality control of the clinical study is another key technique in this project. Grasping the above key technologies will help to develop a scientific and standardized research program at home and abroad, which can provide a

higher level of evidence-based medical evidence for the clinical effect of CTN by EA therapy.

Technical Route：



Statistical Analysis Plan

1. Data entry and storage

1.1 Data entry

(1) The original data collection:

All observation scales will be measured on a "one to one" basis according to the unified standard, and the subject will be completed independently under the guidance of the doctor to ensure complete and correct completion. In the spot, check whether the filling quantity is perfect and accurate. If any omission/review or blurring is found, check the gauge in time and verify the quality of the recovery gauge strictly.

(2) Data entry and statistics：

The Excel spreadsheet is used to record the data and ensure the original data is accurate and reliable. The special personnel shall carry out the statistics and the research managers shall verify the statistical methods, analysis and discussion without error.

1.2 Data storage

(1) The special person is responsible for the management of various documents, and there are special folders for storage in dedicated files, so that the test researcher can view it, and have access and access records.

(2) The test documents shall be protected strictly in accordance with the confidential management principles.

(3) Test file is available for test researchers and relevant researchers view， and other irrelevant personnel shall not be entitled to refer to.

(4) The equipment of storing test files has safety measures such as insect repellent, fire prevention, moisture-proof and anti-theft.

2. Statistical processing

2.1 Analysis data set

(1) Full Analysis Set (FAS):

A collection of all randomly assigned and at least one treated case. When analyzing the main therapeutic indicators, the missing values in the FAS set were

transferred to the current (LOCF) method by using the results observed at the latest time point. The Available Case Analysis principle was used in the Analysis of secondary efficacy indicators, general conditions and safety Analysis.

(2) Per Protocol Set (PPS):

Compliance set refers to meet the inclusion criteria and follow the test protocol to complete the treatment of the set of cases, which is consistent with the test protocol, compliance, did not take prohibited drugs, to complete the evaluation of effectiveness (at least the main outcome) cases.

(3) Security Analysis System (SAS):

At least one treatment is received and the actual data of the safety indicator evaluation record is available.

2.2 Statistical analysis content

The main analysis contents include:

(1) Four groups of cases distribution: Four groups of the total loss rate and the loss due to adverse events off rate comparison.

(2) Comparability analysis: Compare demographic data and other baseline values to measure the comparability of the four groups.

(3) Compliance analysis: The four groups of patients were compared according to the amount of time to receive the appropriate treatment, the program did not use prohibited drugs.

(4) Effectiveness analysis: Main therapeutic indexes are analyzed by PP and ITT simultaneously. Since this study is a multi-center clinical trial, the effect of the central effect and baseline on the therapeutic effect should be taken into account in the analysis.

(5) Effect factor analysis： such as age, gender, duration, combined medication and other factors on the efficacy.

(6) Safety analysis: First, according to the requirements of adverse reaction correlation list describes four groups of adverse events and adverse reactions (including the number of cases of adverse events and laboratory examination indexes before and after the test "normal turn abnormal cases and different rate), statistical

analysis of the adverse reactions by chi-square test.

2.3 Statistical analysis method

(1) The measurement data: First of all, the normality test was used. For normal distribution, the t-test, paired t-test, variance analysis and covariance analysis were used to check the data. For non-normal distributions, using rank sum test and paired rank sum test.

(2) The enumeration data: Using the chi-square test, Fisher exact test and so on. The hierarchical data are analyzed by Ridit, CMH or other non-parametric tests.

(3) Multi-centers analysis of comprehensive efficacy: The CMH method was used for counting data; Analysis of covariance is used for metering data.

(4) All the statistical tests were double-sided, and the p-value is less than or equal to 0.05 and the difference is statistically significant.

2.4 Statistical software

SAS 9.3 software analysis.