Efficacy of acetaminophen with and without oxycodone for analgesia in nonoperative treatment of extremity fractures in adults: Protocol for a double-blind randomized clinical trial

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Study protocol

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Abstract

Background: Opioids and acetaminophen are both widely used to relieve pain after nonoperative treatment of limb fractures, but evidence for superiority of opioids versus acetaminophen is lacking. In this study we aim to determine whether acetaminophen is noninferior to the acetaminophen/oxycodone combination for pain relief after nonoperative fixation of an extremity limb fracture. We hypothesize that acetaminophen is noninferior to the acetaminophen/oxycodone combination. Methods: A double-blind, randomized controlled trial will be conducted. Power analysis determined that 1,226 participants will be needed ($p<0.05$, power 90%). Patients with acute limb fracture who receive nonoperative treatment will be recruited and randomly allocated into two groups: the intervention group will receive oral oxycodone (10 mg)/acetaminophen (650 mg), and the control group will receive acetaminophen (650 mg) only. All participants will be instructed to take one pill of study medication on an as-needed basis and no more frequently than once every 8 hours. The primary outcome measure will be scores on the 11-point Numeric Rating Scale (NRS-11) over 14 days. Secondary outcome measures are scores on the Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), EuroQol five dimensions' questionnaire (EQ-5d), self-rated satisfaction with the analgesia produced, self-reported nighttime sleep duration, number of intervention or control pills used, total duration for taking intervention or control medication. Change of pain scores and the number of times that analgesic drugs were taken in the two groups will be statistically evaluated with t-student tests according to their fracture site. Discussion: This study will be a randomized controlled trial that is adequately powered to test the hypothesis that acetaminophen is noninferior to the combination of acetaminophen and oxycodone in relieving objectively measured pain after nonoperative treatment of limb fractures in adults. It is hopeful to provide a safe and effective analgesic plan for such patients. Trial registration numbers: ChiCTR registry: ChiCTR1800017015 (http://www.chictr.org.cn/showproj.aspx?proj=28612). Registered on 8 July 2018.

Background

Several previous studies concluded that opioids were safe and effective with the outweighed benefits over risks.[1] However, opioid-overdose deaths are increasing every year in the United States (U.S.), and it consisted of large amount of drug overdose deaths at 60.9% in 2014, 63.1% in 2015.[2-4] The crisis of opioid abuse is partially attributed to the overprescription of opioid analgesics,[5 6] highlight the urgent need for evidence on appropriate indication of opioid prescription. A multicenter study in the U.S. showed that 17% of discharged patients in emergency department (ED) were prescribed with opioids and overprescription was in a high incidence.[7]

An epidemiological survey in the U.S. shows that in the past 20 years, the incidence of fractures has increased by 11%, from 3,627/100,000 to 4,017/100,000.[8] It mainly comes from the osteoporosis-related fractures associated with the growth of the elderly population,[9] and traffic-related injuries.[10] The periosteum is a highly innervated tissue surrounding the bone tissues, leading to a moderate to severe fracture-induced pain.[11] Inappropriate pain management greatly increase the risks of chronic pain.[12]

Therefore, appropriate pain relief is important in the management of limb fractures. Opioids and acetaminophen are most widely prescribed to relieve the pain in these patients. However, the prescription of these analgesics was supported by few evidences. According to the suggestion from American Academy of Orthopaedic Surgeons (AAOS), opioids could be prescribed for patients discharged from ED in consideration of sleeping and life quality. A small-scale trial showed that ibuprofen was as effective as oral morphine but produced fewer side effects for fracture pain in children.[13] A large-scale, randomized trial is needed to provide more evidences on this topic with blinding of used analgesics to eliminate the psychological and social bias.

Therefore, we plan to conduct a clinical trial to determine whether the analgesic efficacy of acetaminophen is noninferior to oxycodone/acetaminophen for nonoperative treatment in adults following acute limb fracture. Our larger aim is to provide a safe and effective analgesic plan for such patients. We hypothesize that acetaminophen is noninferior to the combination of acetaminophen and oxycodone in relieving objectively measured pain after nonoperative treatment of limb fractures in adults.

Objectives

This study is a single center, double-blinded randomized controlled trial. The purpose of this trial will be to assess the following:

Whether the analgesic efficacy of acetaminophen is noninferior to oxycodone/acetaminophen for nonoperative treatment in adults following acute limb fracture.

Whether the adverse event rate of acetaminophen is lower than that of oxycodone/acetaminophen for nonoperative treatment in adults following acute limb fracture.

Specific primary objective

The specific primary objective is to determine the decline in NRS pain scores from the baseline to 1, 3, 7, and 14 days after randomized to acetaminophen for nonoperative treatment in adults following acute limb fracture compared to oxycodone/acetaminophen.

Specific secondary objectives

The specific secondary objectives are to determine the change in scores on the SAS, SDS, and EQ-5d, and the patient's satisfaction with the medication (0-10) from the baseline to 14 days after randomized to acetaminophen for nonoperative treatment in adults following acute limb fracture compared to oxycodone/acetaminophen.

Other secondary objectives

Other secondary objectives are to determine the change in the quality and duration of sleep, number of study medications used, duration that analgesics were taken, and adverse events between two groups.

Methods/design

Study setting

This study will be performed in the emergency department (ED) of Shanghai Jiaotong University Affiliated Sixth People's Hospital in China. This hospital is a tertiary and teaching hospital that receives approximately 350,000 ED visits annually. The study was approved by the Ethics Committee of Shanghai Jiaotong University Affiliated Sixth People's Hospital. And we used the SPIRIT reporting guidelines, as Figure 1 shows.

Study design

This study is a single center, double-blinded randomized controlled trial. Figure 2 shows how participants eligible for this trial flow through the study from recruitment to follow-up. Adult patients with a single acute limb fracture occurring less than one day after injury and who are indicated for nonoperative treatment will be recruited. They will be randomly assigned to either the intervention or control group. The intervention group will receive oral pills of oxycodone (10 mg)/acetaminophen (650 mg), and the control group will receive pills of acetaminophen (650 mg) only.

The primary outcome measure will be the 11-point Numeric Rating Scale (NRS-11).[14] Secondary outcomes include Self-Rating Anxiety Scale (SAS),[15] Self-Rating Depression Scale (SDS),[16] EuroQol five-dimension questionnaire (EQ-5d),[17] self-rated satisfaction with the analgesia produced by the intervention or control medication (scale of 0-10), self-reported nighttime sleeping duration, total number of analgesic intervention or control pills used during the trial, total duration for taking intervention or control medication. Any remaining analgesic medications will be collected by the researchers at the end of the trial. Demographic information will be collected from the medical record.

Eligibility criteria

Adult participants will be recruited prospectively and sequentially as they are admitted to the ED of Shanghai Jiaotong University Affiliated Sixth People's Hospital. Informed written consent will be obtained from all participants. All methods and procedures in this study are in accordance with the Declaration of Helsinki.[18]

Inclusion criteria

Male and female patients, 18 to 100 years old, will be candidate participants. We will include patients who have an acute limb fracture diagnosed less than one day after injury. Eligible locations of fractures include foot, ankle, tibia, fibula, knee, femur, hip, hand, wrist, forearm, elbow, humerus, shoulder, or clavicle. All candidate participants indicated for nonoperative treatment and be willing to participate in this study will be enrolled.

Exclusion criteria

Patients with non-limb fractures will be ineligible, or similarly, those who have multiple fractures involving more than one site. Also, patients with vascular, nerve, or tendon injuries, and open fractures will be excluded. Patients with a pre-injury chronic condition requiring frequent pain management such as sickle cell disease, fibromyalgia, or any neuropathy are not eligible, as are those who have taken methadone at any time in their life. Patients who are pregnant, verified by urine or serum HCG testing, will be excluded. Patients who report any adverse reaction or who are allergic to any of the study medications will be dropped from the study. Patients who have contraindications, such as peptic ulcer disease, or who report any prior use of recreational narcotics will be excluded.

Additional exclusion criteria are as follows: medical conditions that might affect metabolism of opioid analgesics or acetaminophen, such as hepatitis, renal insufficiency or failure, hypo- or hyperthyroidism, and Addison's or Cushing's disease; taking any medicine that might interact with any of the study medications, such as anticholinergic drugs, oral contraceptives, loop diuretics, probenecid, or liver enzyme inducers; unable to communicate properly and answer questions (e.g., patients with a diagnosis of dementia); physically handicapped people with mobility problems; people with no fixed domicile and short-term visitors who cannot be easily located; people unwilling or unable to cooperate with data collectors or researchers.

Randomization and blinding

Stratified blocked randomization will be used to group the participants randomly. The fracture site will be a stratification factor, with the following blocks: (1) foot, ankle, tibia, or fibula; (2) knee, femur, or hip; (3) hand; (4) wrist or forearm; (5) elbow or humerus; (6) shoulder or clavicle. The randomization will be carried out by an independent research assistant, who will not be involved in the enrollment, intervention, assessment of the participants, or data analysis. 1226 unique eight-digit random numbers will be generated for each group (total of 6 groups) by SAS® V.9.4 software. The participants will be assigned randomly to two groups (A and B) in a 1:1 ratio according to the designated interval (only the research assistant will know the interval), and the 1226 random numbers will be assigned randomly to the members of each group. Patients of each group will be further categorized according to fracture site, and then the assignments will be documented. These 6 documents (also referred to as the blinding code) contain the participants' serial numbers (according to their order of enrollment), random number sequences, and study group assignment; these will be recorded in duplicate and submitted to the clinical

research-responsible unit and the research assistant for secure storage. Simplified versions of these documents that do not contain the study group will serve as a reference for allocating study medications to participants.

Drug preparation

Each study drug package contains one bottle, and each bottle contains 20 tablets of either oxycodone/acetaminophen or acetaminophen tablets (according to the blinding code). The immediate release oxycodone will be used in this study. The drugs will be contained within identical unmarked, opaque gel capsules. The capsules will be topped up with small quantities of lactose to equalize the weight of the capsules. The shape of the outer packaging and the bottle is exactly the same. A random number sequence will be attached to the outer packet, and there will be a sealed opaque envelope attached (which is called “emergency letter”), which contains study group allocation and medication type contained within the packet. In the event of an emergency, serious adverse reaction, or if the participant needs to know what kind of treatment he/she is receiving, researchers and the participant can obtain the information from the emergency letter. If the seal to the emergency letter is opened and letter is read, the participant will be excluded from the trial.

After data collection is completed, a two-step method is used to reveal group membership. The first step lists only the treatment group to which each participant belongs (such as group A or B), but does not indicate which group is the intervention group or the control group. The second step reveals the treatment received by groups A and B, and which group is the control group. Statistical data analyst will also be blinded to participant allocation.

Intervention

After recruitment, each participant will receive a bottle of tablets according to the random number sequence. The outer package marked with the random number will be tagged with the subject’s serial number, which will be securely stored by researchers for 14 days until the participant’s trial is completed.

All participants will be instructed to take one pill of study medication on an as-needed basis, but to take it no more frequently than once every 8 hours. Any analgesic other than unblinded oxycodone which is administered as a rescue analgesic, is prohibited during the trial. We will complete his/her follow-up unceasingly once a participant took a rescue analgesic, and some extra outcomes including the number of rescue analgesic used and total duration for taking this medication will be recorded. Participants will be encouraged to complete follow-ups, and they will have access to the research team anytime to discuss any issues or concerns during the trial. It will be explained to them that they can discontinue the intervention at any time during the trial. Demographic information of participants who withdraw from the study after randomization and their reasons for withdrawal will be collected.

Assessment

Pain intensity will be assessed by an 11-point numeric rating scale (NRS-11), where “0” is no pain and “10” is worst possible pain imaginable. Administration of the NRS-11 can be conducted over the phone or in person by a hospital staff data collector. By contrast, VAS scoring can be administered only during in-hospital visits. The NRS-11 is as effective as the VAS in assessing acute pain.[19]

Anxiety, depression, and health status and quality of life will be assessed with the following assessment tools. The Self-Rating Anxiety Scale (SAS) is a 100-point test (20 items) that assesses the degree of anxiety. A higher score means greater anxiety. The Self-Rating Depression Scale (SDS) is also a 100-point test (20 items). It assesses the degree of depression. A higher score means that the patient is more depressed. The EuroQol (EQ-5d) is a health description questionnaire that assesses health status and quality of life. It contains two questionnaires comprising five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Along with the EQ-VAS, EQ-5d can evaluate patients’ health status and quality of life.

Outcomes

The primary outcome will be the between-group difference in decline in NRS pain scores from the baseline to 1, 3, 7, and 14 days after randomization. Secondary outcomes include the between-group difference in change in scores on the SAS, SDS, and EQ-5d from the baseline to 14 days after randomization, and on a custom in-house developed question on the patient’s satisfaction with the medication (0-10) at 14 days after randomization. For the latter, “0” is very dissatisfied and “10” is very satisfied. Other secondary outcomes are the between-group difference in change in the quality and duration of sleep, number of study medications used, duration that analgesics were taken, and adverse events.

Data collection

The Additional file 1 presents a complete summary of data collected during the trial. Baseline information will be obtained from the participant, including demographic characteristics, sleep quality during the most recent month at the follow-up, and past medical history before he or she is recruited. General medical examinations will be also conducted by the researcher. The results of the NRS scores will be reported by participants at 0, 1, 3, 7, and 14 days after randomization. The SAS, SDS, and EQ-5d questionnaires will be completed by participants at 0 and 14 days after randomization during in-hospital visits. A nighttime sleeping diary will be recorded by the participants, and then submitted to researchers at 14 days after randomization too. Participants will record the number and the times that analgesic drugs were taken. Adverse events will also be recorded throughout this trial. At the end of trial, we will ask participants which analgesic drugs they believe they took and record it.

Sample size

The sample size was calculated by using the following parameters. An overall 2-sided significance level of 0.05, power of 90% will be calculated. In line with previous studies, only if the between-group change difference of NRS scores is reached 1.3 unit or great, it seems as clinically significant in pain,[14] and the standard deviation of the difference in NRS scores between the two groups was 6.4 points from our prior work. Using these parameters, we calculated a primary sample size of 511 patients per group, giving a total of 1022 patients. Taking into account factors like patients loss-to-follow-up and participant withdrawal during the trial, it is reasonable to increase the sample size by 20%. Therefore, a total number of 1226 participants will be recruited.

Statistical analysis

All analyses will be carried out using SPSS V.16.0 (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc). We will perform an intention-to-treat analysis including all randomized participants, whether or not they obeyed the allocation. Baseline characteristics will be summarized by treatment groups. The results from the trial will be presented as comparative summary statistics (difference in proportions or means), with 95% CIs.

Changes in NRS pain scores (primary outcome); SAS, SDS, and EQ-5d scores; sleep loss; and the number of times analgesic drugs were taken in the two groups will be compared with t-student tests, according to their respective fracture site. The incidence of adverse events in the two groups will be presented as proportions and will be compared using χ^2/Fisher's exact test.

Safety and adverse event reporting

We will record all adverse events observed by researchers or participants that occurs within the14 days of randomization, whether they could be related to the study medication or not. Once adverse events occur, participants will cease study medications and we will try our best to collect their data. If serious adverse events occur, the investigator will complete the serious adverse event report form (SAE) immediately, and inform the research group within 24 hours. If it isn't a life-threating event and is thought to be an accident related to the study medication, we will notify the research ethics committee (REC) within 15 days. The research ethics committee will be notified within 7 days for a life-threatening event. All these adverse events will be reported to the ethics review committee at the next meeting. All participants who experienced adverse events will be followed up until the end of the trial.

Patient and public involvement

In a pilot study, we selected patient representatives to help develop and refine our research project. Because of their complaints about the obvious deterioration of sleep after a fracture, we added "change

of sleep quality and duration" as an indicator to evaluate it as a contributor to analgesic efficacy. The idea of treating the fracture sites as a stratification factor also came out of the pilot study.

Discussion

Opioid-involved overdose deaths are increasing at an alarming rate, and this is becoming more common worldwide. Many of these are related to the large amount of opioids being consumed [2-4]. At least for the case of acute pain related to limb fractures, a simple solution would be to reduce opportunities of opioid overconsumption by prescribing an alternative—equally effective—less dangerous analgesic drug. The data to date are confusing and inconsistent about the relative efficacy of opioids and acetaminophen for treating acute pain from limb fractures. These data make it difficult for Orthopaedic surgeons to implement a safe and effective plan for pain management in nonoperative treatment of limb fractures.

Strengths of this study include its large number of study subjects drawn from a large metropolitan hospital specializing in Orthopaedics, its design as a prospective randomized controlled trial, use of multiple widely used objective measures of experienced pain and anxiety, and the short duration of the trial. Specially, blinding is very important that all of the outcomes are objective.

The major limitation is that the trial is being conducted at a single healthcare center in China. Another limitation is that all outcomes in this study are the patient-reported by themselves, thus, potential reporting bias is clearly inevitable.

In conclusion, this study is a randomized controlled trial that is adequately powered to test the hypothesis that acetaminophen is noninferior to the combination of acetaminophen and oxycodone in relieving objectively measured pain after nonoperative treatment of limb fractures in adults. At the conclusion of this trial, we will have an answer to the straightforward question: Can fracture-related pain relief be achieved sufficiently with the use of acetaminophen alone?

Trial Status

The trial protocol (version 3.0, 7.5.2018, as Additional file 4 showed) was reviewed and approved by the ethical review committee of the Shanghai Jiaotong University Affiliated Sixth People's Hospital in 31.5.2018. This study started recruiting patients in November 2018. The predicted study recruiting end-date is November 2019.

Abbreviations

AAOS: American Academy of Orthopaedic Surgeons; ED: emergency department; EQ-5D: EuroQol five dimensions questionnaire; NRS-11: 11-point Numeric Rating Scale; REC: research ethics committee; SAE: serious adverse event; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; U.S.: United States.

Declarations

Ethics approval and consent to participate

This trial is registered in the Chinese Clinical Trial Registry (ChiCTR1800017015), and the Additional file 2 presents the registration data set of this trial. We obtained full ethical approval for this study from the ethical review committee of the Shanghai Jiaotong University Affiliated Sixth People's Hospital (protocol number: 2018-024-(2)), presented by the Additional file 3. All relevant amendments have been assessed and approved by the ethical review committee of the Shanghai Jiaotong University Affiliated Sixth People's Hospital. Before recruitment commences, the ED our hospital will have received the authority to recruit subjects.

The trial will be conducted in accordance with the principles of Good Clinical Practice and relevant regulations. The informed consent form explains in full detail the aims and objectives of the study, selection criteria, and the planned processes of this trial will be shared with patients before recruitment. The research team will provide an individual face-to-face consultation with all participants to answer any questions they may have. Full written informed consent will be obtained from all participants.

Consent for publication

Not applicable.

Availability of data and material

The authors will submit the findings of the study to peer-reviewed journals. The raw data obtained in this clinical trial will be disseminated to patients and the public via the Research Manager website (http://www.medresman.org) 6 months after the end of the trial.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XYZ and HYZ conceived the idea. XYZ supervised this study and is the guarantor. HYZwas responsible for study design. CQZ, YMC, CG, XZZ, BBB, XWL and JQL were involved by constructive suggestion. TG prepared draft manuscript. XYZ revised the manuscript. XYZ carried out the statistical calculation. HYZ is the co-first author. All authors approved submission of this manuscript.

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Figures

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Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10,11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13,14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13,14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n/a
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14,15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14,15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14,15
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Figure 1

Reporting checklist for protocol of a clinical trial.

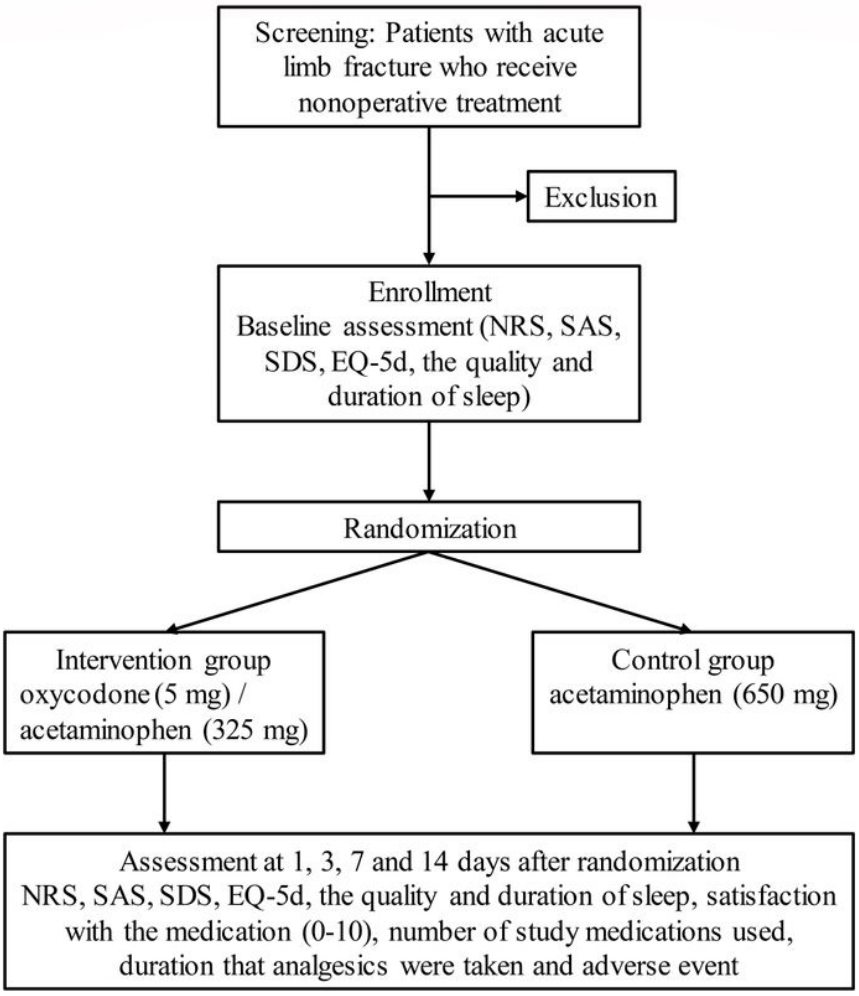

Figure 2

Flow chart of this trial.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.docx
- supplement2.docx
- supplement3.docx
- supplement4.doc