Comparison of Oxycodone and Sufentanil for intravenous patient-controlled analgesia after hip surgery: a prospective, randomized controlled trial

CURRENT STATUS: POSTED

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DOI: 10.21203/rs.2.11027/v1

SUBJECT AREAS
- Anesthesiology & Pain Medicine
- Orthopedic Surgery

KEYWORDS
- Randomized controlled trial, oxycodone, sufentanil, patient-controlled analgesia, hip surgery
Abstract

Background

Intravenous patient-controlled analgesia (PCA) after hip surgery should be focused on the balance of sufficient analgesia and the risk of associated adverse reactions. Sufentanil has high analgesic efficacy as a common used drug for PCA while with obvious side effects. Oxycodone is a semi-synthetic opioid which has been reported to have good analgesic effect and lower incidence of adverse reactions related to long-acting opioid. We hypothesize that in hip surgery, compared with sufentanil PCA, the equipotency dose of oxycodone PCA could achieve the same postoperative analgesic efficacy and may also reduce the incidence of adverse reactions associated with long-acting opioids.

Methods/Design

This trial is a prospective, randomized, controlled clinical trial comparing the safety and efficacy of oxycodone and sufentanil for postoperative patient-controlled analgesia in patients undergoing hip surgery. A total of 570 subjects undergoing hip surgery will be randomly allocated to either sufentanil PCA group or oxycodone PCA group. The primary outcome is the resting numerical rating scales (NRS) pain scores at 30 min, 2 h, 6 h, 24 h, 48 h, and 72h after surgery. The secondary outcomes include postoperative NRS pain scores on movement, in-hospital complications, range of motion of hip joints, mobilization time, length of hospital stay, total in-hospital cost, and readmission rate by 30 days after discharge from the hospital.

Discussion

This trial is designed to compare the safety and efficacy of oxycodone and sufentanil PCA in patients undergoing hip surgery, in order to find an optimal postoperative analgesic regime with fewer adverse reactions and promoting patients’ rehabilitation. The results will provide evidence for anesthetic choice in clinical practice.

Background

Hip surgery is a common type of orthopedic surgery. The pathologies are complex, including chronic conditions such as femoral head necrosis, primary hip dysplasia, hip joint osteoarthritis and
rheumatoid arthritis, as well as acute diseases such as femoral neck fractures and intertrochanteric fractures. The surgical treatment includes closed reduction and internal fixation, open reduction and internal fixation, hemiarthroplasty (femoral head replacement), and total hip arthroplasty, etc. The population of patients undergoing hip surgery has a high proportion of elderly (>65 years old), with multiple preoperative comorbidities, and significant postoperative pain. We must achieve the balance between the providing sufficient analgesia and minimizing associated adverse reactions perioperatively for such group of patients, therefore promoting patients’ rehabilitation. [1, 2]

Sufentanil, a pure μ receptor agonist with active metabolite, is a long-acting strong opioid which has high analgesic efficacy. It is commonly used in anesthesia practice, not only for intraoperative analgesia, but also postoperative pain relief, i.e. a popular drug of choice used for patient-controlled analgesia (PCA) [3]. However, as a long-acting opioid, sufentanil is associated with high incidence of postoperative nausea and vomiting (PONV), respiratory depression and other adverse reactions, which could negatively affect the patient's analgesic satisfaction, and compromise the course of postoperative recovery. It is important to establish an effective and safe postoperative analgesic regime that can achieve the comparable analgesic efficacy with reduced incidence of adverse reactions [4]. Oxycodone is a semi-synthetic opioid which is extracted from the thebaine, it activates both μ and κ opioid receptors. It has been reported to have good analgesic effect and lower incidence of adverse reactions such as PONV in comparison with morphine, and could be a reasonable option for PCA [5]. As oxycodone can agonize κ receptors and reduce visceral pain, most of the existing studies on oxycodone are focused on laparoscopic cholecystectomy and other abdominal surgeries, with the average age of study patients is between 40 to 55 years old, and also lack of large sample studies [6,7].

Based on these literatures, we hypothesize that in hip surgery, compared with sufentanil PCA, the equipotency dose of oxycodone PCA could achieve the same postoperative analgesic efficacy and reduce the incidence of adverse reactions associated with long-acting opioids. We design this randomized controlled trial to compare the safety and efficacy of oxycodone and sufentanil for PCA in patients undergoing hip surgery, in order to find an optimal postoperative analgesic regime with
fewer adverse reactions and promoting patients’ rehabilitation.

Methods/design

Trial Design

This trial is a prospective, randomized, controlled clinical trial comparing the safety and efficacy of oxycodone and sufentanil for postoperative patient-controlled analgesia in patients undergoing hip surgery, and it will be executed in general hospitals in China and Singapore. It has been registered on http://www.clinicaltrials.gov, with the registration number: NCT 03685188 on September 13th, 2018. It will be conducted according to rules of the Declaration of Helsinki. A brief flow diagram of the trial under the guidance of Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org/) is summarized in Figure 1, and a checklist of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) is provided in Figure 2.

This trial is supported by grant from the West China Hospital scientific research project (HX-H1810182) supported by Chinese Research Hospital Association, the Key research and development (R&D) Program of Science & Technology Department of Sichuan Province (2019YFS0224), and the National Natural Science Foundation of China (81502722). There is no conflict of interests. The study team, including anesthesiologists, orthopedic surgeons, clinical research coordinators, research nurses, and ward nurses will be trained with a training manual before starting the trial.

Fig. 1 Flowchart for participant eligibility, interventions, assessments and follow-up

Fig. 2 Standard Protocol Items: Recommendations for Interventions Trials (SPIRIT) figure (numbers beside t represent days)

Sample size calculation

The primary hypothesis of this trial is that the analgesic effect of oxycodone PCA is not inferior to the equipotency dose of sufentanil PCA, and the incidence of PONV is lower in oxycodone PCA than in sufentnail PCA during postoperative period. Therefore, the effect of postoperative analgesia is considered as one primary outcome and compared between groups with non-inferiority design, and
the incidence of PONV is another primary outcome and compared with superiority design. According to preliminary observation, for the primary outcome of postoperative analgesia, the mean numerical rating scales (NRS) pain score of patients receiving sufentanil PCA and oxycodone PCA at 30 minutes after operation were 3.5 and 3 respectively, with a common standard deviation of 0.866. So we conservatively assumed that the difference in NRS between the two groups is 0 and the common standard deviation is 0.866. We chose the non-inferior margin as 1/10 of the mean value 0.3, assuming the difference between two groups at a 2.5% significance level and a power of 0.80, 132 subjects are required in each group. Considering an estimated 20% dropout rate, 165 subjects in each group, and a total of 330 subjects are required. For the primary outcome of incidence of PONV, it is reported to be 38.8% in sufentanil and 25.3% in oxycodone [9]. Assuming the difference between two groups at a 2.5% significance level and a power of 0.80, 223 subjects are required in each group. Considering an estimated 20% dropout rate, 279 subjects in each group, and a total of 558 subjects are required. We plan to enroll 570 subjects in this study.

Randomization and blinding

A Central Randomization System (CRS) will be applied to randomize the subjects. According to the sequence of time that the subjects are enrolled, after entering the subject’s information, the randomized number and allocated group could be retrieved on the website of the CRS. The trial is designed as prospective randomized clinical trial. After obtaining the random number of the patients in the central randomized system (http://www.medresman.org/login.aspx), the researchers or the clinical research coordinators will inform the research nurses to formulate the study drugs into 100ml patient-controlled analgesic pumps according to the study group. The pump will be given to the clinical investigators before the operation. In China, both sufentanil and oxycodone are controlled drugs, and patient who receive treatment of these drugs must be registered with real name, and these drugs must be marked and labelled on the patient-controlled analgesic pumps. So the researchers, the patients, and the clinical staffs know the group allocation, but the follow-up personnel, and the statisticians are blinded to the group allocation.

Study organization and quality control
The implementation of the study, the data completeness and accuracy will be supervised by Department of Anesthesiology of West China Hospital and the Office of Scientific Research at West China Hospital. Dr. Ren Liao will be the alert personnel of serious complications. Data collection and follow-up will be performed by clinical research coordinators. The data safety and monitoring board, including a statistician, an ethicist, an orthopedic surgeon, an anesthesiologist, and an internal physician who are not unrelated to this trial, will be involved for the entire duration of the trial to review all investigational data for accuracy and completeness periodically to ensure protocol compliance. There are no stop rules in this study, and no preliminary analysis will be performed before the completion of the study.

Interventions

After admission, preoperative examinations will be arranged according to the routine arrangements of participating hospitals. Vital signs including electrocardiogram, blood pressure, and pulse oximetry will be monitored during operation. General anesthesia, epidural, spinal, or combined epidural-spinal anesthesia, or nerve block could be applied for the surgery, but indwelling catheter for postoperative analgesia should be avoided if epidural or nerve block anesthesia has been chosen. Antiemetic drugs (such as granisetron, ondansetron, tropisetron, etc.) should be given 30 minutes before the end of the operation, and local anesthetics or cocktails for incision infiltration can be applied according to the routine of participating centers.

According to the analgesic formula of postoperative patient-controlled analgesia, the subjects are randomly divided into Oxycodone group and Sufentanil group.

Oxycodone group: PCA is formulated at 0.4 mg/ml of oxycodone.

Sufentanil group: PCA is formulated at 2 μg/ml of sufentanil.

No background dose will be applied for PCA in both groups. When the subject feels the pain, he could activate the analgesic pump to infuse 2 ml of analgesic drugs. The lock-out time is 12 minutes and the maximum times the pump could be activated are 5 times per hour.

Recruitment

A total of 570 patients undergoing hip surgery will be enrolled at West China Hospital of Sichuan
University.

Enrollment criteria

Inclusion criteria

· Patients undergoing unilateral hip surgery, with both genders;
· Age above 18 years;
· Informed consent signed.

Exclusion criteria

· Pregnancy or lactating;
· History of drug abuse, including but not limited to opioids, amphetamines, ketamine, etc.;
· History or family history of malignant hyperthermia;
· Known allergy to opioids or any other anesthetic agent;
· History of nervous system diseases such as peripheral neuropathy, or psychiatric mental illness, or postoperative delirium;
· Other conditions that the investigators consider unsuitable for participation in the study, such as Parkinson's disease, unable to communicate, or impairment of cognitive function;
· Participation in another trial in the past three months.

Exit criteria

Subjects enrolled in this study have the right to decline further participation at any time of the study without giving any reason, and the participation will be terminated immediately once the subject raises the request. On the other hand, the investigators can terminate the study for the participant at any time during the study. If a subject develops any kind of condition that meets the exclusion criteria during the study, or if the patient's safety is compromised, the study must be terminated immediately.

Preoperative visit and evaluation, informed consent form

All patients scheduled for hip surgery will be screened on the day of hospitalization. We will take the general information about the patient, current and past medical history. We will also assess the patient’s eligibility based on the pre-determined inclusion criteria, and exclusion criteria. For the
eligible patient, the clinical research coordinator will present the “informed consent form” to explain our study in details, and inform the subject that he is free to withdraw his consent from this trial at any time. Written informed consent form shall be obtained from each subject.

Outcome measures

Primary outcome

i. The resting numerical rating scales (NRS) pain scores at 30 min, 2 h, 6 h, 24 h, 48 h, and 72h after surgery.

ii. The incidence of PONV.

Secondary outcomes

i. Postoperative NRS pain score on movement during 3 days after operation.

ii. Time from the end of operation to the first onset of PONV (hours).

iii. The severity of first PONV and the most severe PONV, which is scored from 0 to 10, and 0 represents no PONV at all, and 10 represents very severe PONV.

iv. In-hospital complications, which are divided into five grades:

a. Grade I: Recovery after temporary treatment, e.g., postoperative anxiety, insomnia.

b. Grade II: Prolonged hospitalization, e.g., pulmonary infection requiring antibiotics or other treatment, surgical wound infection requiring wound debridement.

c. Grade III: Life threatening complications requiring intense treatment during hospitalization, and resulting in good functional recovery e.g., dialysis therapy for acute renal insufficiency, mechanical ventilatory support for respiratory failure, or postoperative bleeding requiring re-operation.

d. Grade IV: Life threatening complications resulting in significantly decreased quality of life, e.g., myocardial infarction, stroke that left with paralytic limbs.
e. Grade V\[All-cause mortality by 30 days after operation, which is defined as a secondary outcome.

v. Range of motion of hip joints during 3 days after operation.

vi. Straight leg raising time, defined as the time from the end of operation to the time that patient can raise his affected lower limb by himself (Unit: hour).

vii. Groundexercise time, defined as the time from the end of operation to the time that patient can do the ground exercise by himself (Unit: hour).

viii. Mobilization time, which is defined as the time frame from the end of operation to able to walk without external assistance (Walking aids such as crutches can be used, unit: hour).

ix. Residual amount of drug in the analgesic pump.

x. Postoperative analgesics requirement during 3 days after operation.

xi. Total in-hospital cost.

xii. Length of stay (LOS) in hospital, which is defined as time frame from the day of hospital admission to discharge from the hospital (Unit: day).

xiii. Postoperative hospital stay, which is defined as time frame from the day of operation to discharge from the hospital (Unit: day).

xiv. Readmission rate by 30 days after discharge from the hospital.

Statistical analysis

All outcomes will be analyzed by using SPSS18.0 software (Statistic Package for Social Science, SPSS, Inc., Chicago, IL, USA) with intent-to-treat analysis. The repeated measurement variance analysis will be used to compare the resting NRS pain scores at 30 min, 2 h, 6 h, 24 h, 48 h, and 72 h after the surgery, as well as NRS pain scores on movement from day 1 to day 3 after operation. The quantitative data will be tested for normal distribution, for example, the total hospitalization days, days of postoperative hospital stay, total hospitalization expenses, etc. The data in accordance with
the normal distribution is presented as mean ± standard deviation, the analysis is performed by using the Student-t test. The data of the non-normal distribution is presented as the median (minimum, maximal), and the comparison between groups are performed by Kruskal-Wallis tests. The Z test will be used to compare the incidence of PONV, postoperative adverse reactions, and the incidence of re-admission within 30 days after surgery. The T test will be used to compare the dosage of postoperative analgesics which been used by the patients. P < 0.05 indicates a statistical difference. For the primary outcome, we will perform subgroup analysis based on group differences. Subgroups are defined by age (<65, ≥65), gender (Male, Female), acute trauma (from injury time to surgery time <14 days) or chronic joint disease (disease course >1 year), and whether regional or local anesthesia (including epidural, spinal anesthesia, nerve block, and local infiltration) applied. Analyses will be performed for each subgroup in a similar way to the primary analysis. Forest plots will be draw based on the odds ratios and corresponding 95% confidence intervals.

Discussion

Pain is one of the major factors limiting early mobilization after hip surgery, resulting increased risks of thromboembolism and infection, or delayed postoperative rehabilitation, especially for the elderly patient [9,10]. Appropriate pain management is crucial, and there are several choices of techniques for postoperative analgesia including epidural block, peripheral nerve block, transdermal administration, and intravenous analgesics infusion. However, patient-controlled analgesia, including epidural PCA and intravenous PCA, is increasingly applied in hospitals. From the concept and requirement of enhanced recovery after surgery (ERAS) [11], we need to provide a sufficient analgesia with reduced side effects while conserving the ability to mobilize. The techniques of epidural or nerve block such as fascia iliaca compartment block or femoral nerve block could provide reliable analgesia, but they are associated with motor blockage, which results weakened lower leg muscle strength and limits mobilization [12,13]. Therefore, in this trial, we choose intravenous PCA so as to conserve the muscle strength.

Intravenous PCA with opioids has been applied in clinical practice for more than thirty years [14]. Physicians like to choose a continuous infusion of opioids such as morphine, fentanyl, or sufentanil to
improve analgesia efficacy. However, serious complications associated with PCA with long-acting opioids have been reported [15], which lead to restriction of application of PCA, even drawback of PCA. For instance, in Department of Orthopedics of West China Hospital, more than 10,000 cases were done every year, but less than 5% patients accepted intravenous PCA after operation. The inquiry for postoperative care of the orthopedic patients showed that the patient would rather bear the pain than experience nausea, vomiting, or dizziness. If we change the mode of PCA from continuous infusion (background analgesia) to PCA without background analgesia, that means if the patient does not feel pain, there’s no analgesic delivered into his venous line; but whenever the patient feels pain, he pushes the button of an electronic analgesic pump, then a fixed amount of an analgesic is delivered directly into the venous line, the adverse reactions should be decreased theoretically. Another way to provide analgesia with decreased side effects is application of other medications. Oxycodone has been reported to be associated with lower incidence of PONV than sufentanil in different clinical setting [16,17], so we hypothesize that oxycodone PCA can provide a non-inferior effect of analgesia as the equipotency dose of sufentanil but with decreased incidence of adverse reactions in patients undergoing hip surgery.

In summary, this trial is designed to test the hypothesis that oxycodone PCA could achieve the same postoperative analgesic efficacy as the equipotency dose of sufentanil PCA, and oxycodone may reduce the incidence of adverse reactions associated with sufentanil after hip surgery.

Trial Status
The version of the study protocol is 1.0 of 11 March 2018. The first investigators’ meeting was held on 1 December 2018. Recruitment of subjects started on 1 March 2019, and the first subject was enrolled on 7 March 2019. Recruitment is expected to be completed in December 2021.

Abbreviations
ASA: American Society of Anesthesiologists; CONSORT: Consolidated Standards of Reporting Trials; CRS: Central Randomization System; ERAS: enhanced recovery after surgery; LOS: length of stay; NRS: Numerical rating scales; PACU: Post anesthesia care unit; PCA: patient-controlled analgesia; PONV: postoperative nausea and vomiting; SPIRIT: Standard Protocol Items: Recommendations for
Declarations

Acknowledgements

Special thanks to all participants in this study.

Funding

This study is supported by grant from the West China Hospital scientific research project (HX-H1810182) supported by Chinese Research Hospital Association, the Key research and development (R&D) Program of Science & Technology Department of Sichuan Province (2019YFS0224), and the National Natural Science Foundation of China (81502722). The funding bodies had no role in trial designing, and will not have any role in trail execution, data analysis and interpretation, and the manuscript submission for publication.

Availability of data and materials

The individual participant data with anonymity will be uploaded in the IPD sharing platform to achieve the data sharing, and will be available after the Principle Investigator’s agreement on reasonable request.

Authors’ contributions

RL led the study design and will be responsible for subjects’ recruitment in China. JYL searched related literature, developed the study protocol, drafted the manuscript, and will be responsible for follow-up. HBZ revised English grammar of manuscript, and will be responsible for subjects’ recruitment in Singapore. All the authors have reviewed the manuscript and approved the final version.

Ethics approval and consent to participate

Central ethical approval has been confirmed after reviewing the protocol version 1.0 from the Biological-Medical Ethical Committee of West China Hospital, Sichuan University on 26th of April, 2018 (ref approval no. 2018-86) and we will not begin recruiting at other centres in the trial until local ethical approval has been obtained.

At the preoperative interview, the researchers or the clinical research coordinators will explain to the
potential participants about details of the trial. For the eligible subject, a written informed consent form must be provided prior to enrollment of this study, and the privacy of any participant will be protect strictly. During the process of trial execution, data collection and analysis, any confidential information will not be exposed. All the participants are free to withdraw from this study at any time without any reason.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures
Eligibility assessment
• Patients undergoing hip surgery, with both genders.
• Age above 18 years.

Assessment visit

Eligible \( \rightarrow \) Randomization

Ineligible \( \rightarrow \) Discharge from study

Intervention

Oxycodone group \( N=285 \)

Sufentanil group \( N=285 \)

1:1

Follow-up

Intend-to-treat analysis
Primary outcome: Numerical rating scales (NRS) scores at rest 30 min, 2h, 6h, 24h, 48h, and 72h after operation.
Secondary outcomes:
• NRS scores during mobilization or physical therapy during 3 days after operation.
• In-hospital complications.
• Postoperative Oxycodone and sufentanil requirement during 3 days after operation.
• Length of hospital stay.

Figure 1
Flowchart for participant eligibility, interventions, assessments and follow-up

| STUDY PERIOD | Enrollment | Allocation | Post-allocation | Closeout |
|--------------|------------|------------|-----------------|----------|
| **Time point*** | -t<sub>1</sub> | 0 | t<sub>1</sub> | t<sub>1+3</sub> | t<sub>1+30</sub> | t<sub>x</sub> |
| **ENROLLMENT:** | | | | | | |
| Eligibility screen | | | | | | × |
| Informed consent | | | | | | × |
| Allocation | | | | | | × |
| **INTERVENTIONS:** | | | | | | |
| Intervention | | | | | | |
| Oxycodone group | | | | | | ←→ |
| Control | | | | | | ←→ |
| Sufentanil group | | | | | | ←→ |
| **ASSESSMENTS:** | | | | | | |
Figure 2

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure
(numbers beside t represent days)

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
2019-06-02--Trials-SPIRIT-Checklist.doc