Equivalent doses study of nalbuphine and sufentanil for colonoscopy under bispectral index monitoring

Chaoyi Deng,Xiao Wang,Qianmei Zhu,Yanming Kang,Jinlin Yang,Heng Wang

Abstract

Backgroud:

Since sedation and analgesia are widely accepted by patients and even considered by many gastroenterologists as an integral component of the endoscopic examination, opioids are indispensible in managing pain. Nalbuphine is as effective as morphine as a perioperative analgesic but has not been compared directly with sufentanil in clinical trials.

Objectives

The aims of this study were to compare the efficacy and safety of nalbuphine with that of sufentanil in patients undergoing colonoscopy and to determine the optimal doses of nalbuphine in this indication

Methods

Two hundred and forty consecutive patients aged 18–65 y with an American Society of Anesthesiologists classification of I–II and scheduled for colonoscopy were randomized to receive sufentanil 0.1 μg/kg (group S), nalbuphine 0.1 mg/kg (group N1), nalbuphine 0.15 mg/kg (group N2), or nalbuphine 0.2 mg/kg (group N3). Baseline vital signs was recorded before the procedure. The four groups were monitored for propofol sedation using the bispectral index and pain relief was assessed using the Behavioral Pain Scale for non-intubated patients. The incidences of respiratory depression during endoscopy, nausea, vomiting, drowsiness, and abdominal distention were recorded in the post anesthesia care unit at 24 and 48 h after colonoscopy.

Citation: Chaoyi Deng,Xiao Wang,Qianmei Zhu,Yanming Kang,Jinlin Yang,Heng Wang Equivalent doses study of nalbuphine and sufentanil for colonoscopy under bispectral index monitoring. **protocols.io**

dx.doi.org/10.17504/protocols.io.iq4cdyw

Published: 14 Jul 2017

Protocol

Background

Step 1.

Colonoscopy is the most important and reliable method for the diagnosis and treatment of lower digestive tract diseases. But colonoscopy long operation time, strong stimulation, especially the bowel gas injection and was pulling the hand, nausea, pain, and even intestinal loop or intestinal spasm, elevated blood pressure, heart rate, and even induce angina, myocardial infarction, stroke or cardiac arrest and other serious complications; on the other hand, bring tension anxiety and fear to patients,

a few patients can not tolerate and with the completion of endoscopic procedures, so that doctors cannot clearly endoscopic diagnosis and treatment of related diseases. At present, a lot of units in our country have already carried out sedation and anesthesia in endoscopic diagnosis and treatment. Endoscopy of the sedation / anesthesia is through the application of sedative and narcotic analgesics and related technology, to eliminate or reduce endoscopy or during the treatment of pain, abdominal distension, nausea and vomiting and other subjective pain and discomfort, especially can eliminate the fear of patients to check again, to improve the patients of digestive endoscopy acceptance, and create better conditions for the diagnosis and treatment of endoscopic doctor.[1]

At present the common clinical moderate or deep sedation, intravenous injection of fentanyl or sufentanil (3050ug) (35ug) and (or) a small dose of midazolam (12mg), and then given 12mg/kg of propofol or etomidate 0.20.3mg/kg. The patient's spontaneous breathing was slow but steady, the eyelash reflex disappeared, the whole body muscles relaxed, and the jaw was unresponsive. If the diagnosis and treatment for a long time or the operation of a strong stimulus, according to patients with signs such as deep breathing, heart rate, and body movement, every vein of propofol or etomidate 0.20.5mg/kg 0.1mg/kg, until the end of inspection. [1] propofol has an inhibitory effect on the circulation and upper airway reflex and leads to the patients with no intention to exercise. So, do not recommend medication as independent, clinical application combined with opioids and propofol with high success rate, but respiratory depression, apnea, hypotension, dizziness, abdominal distension and pain after the examination is still the main side effects.[2]

Nalbuphine hydrochloride [(-) -17 (cyclobutylcarbinyl) -4,5 alpha epoxy morphinans -3,6 alpha, 14-three ethanol hydrochloride is kappa agonist] / mu receptor antagonist analgesics, pain control and morphine, for the treatment and prevention of moderate to severe pain. No cardiovascular side effects of nalbuphine, respiratory inhibition is also slightly, and the ceiling effect. Nalbuphine usually 2 3 minutes of onset, 30 minutes to reach the peak, can maintain 3 6 hours analgesia, ceiling effect dose of 0.3 0 5mg /kg.

Foreign studies show that intrathecal nalbuphine combined with morphine reduces the side effects of opioids and does not affect postoperative analgesia. [3] can also be associated with the high proportion of bupivacaine intrathecal nalbuphine and propofol for surgical abdomen, urinary system and lower extremity induction for laryngeal mask airway insertion of [2] on domestic nalbuphine little research, Yu Yang said in 1992 that nalbuphine for outpatient anesthesia. Study on pharmacokinetics of [4]2011 Cai Lijing of nalbuphine injection in healthy subjects. [5]2013 Li ring compared dezocine and morphine and nalbuphine for patients with postoperative analgesic effect. [6]

Nalbuphine is not in the excitement of narcotic drugs and psychotropic drugs in the list, can be used as non narcotic drugs excited storage, and based on the basis of routine prescription application. [7] this is also expected to solve the problem of the use of propofol for sedation in our country due to the restriction of fentanyl family. In addition, because of its unique role and mechanism of moderate sedation analgesia, preoperative application of nalbuphine 0.1-0.2mg/kg can relieve the pain, bring calm and stability.

Aims and objectives

Step 2.

The aims of this study were to compare the efficacy and safety of nalbuphine with that of sufentanil in patients undergoing colonoscopy and to determine the optimal doses of nalbuphine in this indication.

Trial method

Step 3.

We carried out a prospective, randomized, and doubled-blinded clinical trial.

Study population

Step 4.

Inclusion criteria

(i) aged 18-65 years;

(ii) body mass index(BMI) 18.5-30 kg/m2;

(iii) American Society of Anesthesiologists(ASA) classification of I-II;

(iv) the duration time of colonoscopy<30min.

Exclusion criteria

(i) a history of abnormal recovery from anesthesia;

(ii)a heart rate on electrocardiography of <60 beats/min;

(iii) systolic blood pressure(SBP)>180mmHg or SBP<90mmHg;

(iv) acute airway inflammation in the previous 2 weeks;

(v) neuromuscular disease;

(vi) possible or confirmed difficult airway;

(vii) a suspected history ofabuse of narcotic analgesics or sedatives;

(viii) a history of allergy to propofol or opioids;

(ix)an inability to communicate.

Dosage regimen

Step 5.

All the patients fast 8h,water 2h before trial,and no other preoperative medication. With 22G needle to build venous channel in their right arm and All patients were given supplemental oxygen intranasally (5 L/min) and continuous monitoring for HR (three-lead electrocardiogram), oxygen saturation (pulse oximetry), blood pressure (automated blood pressure cuff, serial measurements every 3 minutes) , SpO2, BIS (BIS vista monitoring system) Respiratory rate(RR) and end-tidal CO2(ETCO2), easy backup anesthesia machine, ventilator,rescue,etc.

Patients received either sufentanil or nalbuphine. Propofol was initially administered at a rate of 1ml (10mg)/5 seconds to maximum dose of 4 ml(40mg), if body weight□60kg, or 5ml(50 mg), if body weight□60kg. Additional doses (20□30mg) of propofol were administered if the patient began to move, or if the BIS value started rising to 80.

Allocation	Dosage regimen
S	- 0.1ug/kg sufentanil+ propofol
N1	- 0.1mg/kg nalbuphine+ propofol
N2	- 0.15mg/kg nalbuphine+ propofol
N3	- 0.2mg/kg nalbuphine+ propofol

Observational index

Step 6.

A)**general index**

Age, height, weight,sex,blood pressure,heart rate and blood test and ECG (if have), past medical history, history of anesthesia and the diagnosis.

B)**Main evaluation index**

Evaluation of colonscopy insert, splenic flecure, hepatic flecture conditions(smooth)

1. Resistance to insert: no/mild/obvious;
2. The facial expression: no/mild/obvious;
3. The body/head movement: no/light/obvious.

C) **The secondary evaluation index**

(1)Time

Time: began with a stopwatch to record time,record the induction time, wake up of time, normal life and work.

(2)The total propofol dose□induction□maintaince□

(3)frequency of bowel movements

(4)Baseline vital signs□

Blood pressure，Heart rate，

oxygen saturation(SPO2%)，every 1min for the first 3 min after induction and every 3 min thereafter，

(5)VAS

VAS score method:Use a scale of 10cm long,with10 scale both ends are respectively 0 points and 10 points, to let the patients in the ruler can represent their pain degree of the corresponding position, along with the visitors according to mask the location of the patient for the score. VAS score range of 0-10;0mean painless,1-3 points mean slight pain，4， 6 points mean moderate pain, and 7-9 points mean severe pain

Record VAS before the procedure and then in the Post Anesthesia Care Unit.

(6)Side effects

Intraoperation:hypotension, low oxygen saturation, airway obstruction, respiratory depression, apnea, bradycardia, tachycardia, body movement.

Postoeration: cold/hot, nausea, vomit, nightmare, drowsiness, puritus, abdominal pain.

(7)Satisfaction:patients; physicians;anestheist

D)**Postoperative observation index**

Modified Aldrete Score
Activity ☐ 2=Able to move 4 extremities voluntarily or on command ☐ 1=Able to move 2 extremities voluntarily or on command ☐ 0=Able to move 0 extremities voluntarily or on command
Respiration ☐ 2=Able to deep breathe and cough freely ☐ 1=Dyspnea or limited breathing ☐ 0=Apneic
Circulation ☐ 2=BP +/- 20% of Preanesthetic level ☐ 1=BP +/- 20-50% of Preanesthetic level ☐ 0=BP +/- 50% of Preanesthetic level
Consciousness ☐ 2=Fully Awake ☐ 1=Arousable on calling ☐ 0=Not responding
Color ☐ 2=Pink ☐ 1=Pale, dusky blotchy, jaundiced, other ☐ 0=Cyanotic
Total points，

Statistical Analysis

Step 7.

Sample calculation

This test according to the main evaluation index minimun pulse oxygen saturation sample size estimation, positive control was used with statistical analysis using analysis of variance or nonparametic test. Estimated formula for n=2[(Z1-alpha+Z1-beta)(S/g)]2,the alpha 0.025,beta of 0.2.according to the literature,the lowest oxygen saturation difference between the two groups about the delta=4%,S=6.93, compute the number of cases in each group of 48 cases. Considering the loss rate and other factors,the clinical trial design 60 cases in each group, a total of 240.

FAS, full analysis set

According to the principle of ITT(Intention-to-treat),all the randomized groups,using at least one study medicine,with cases of evaluated data, which constitute FAS. Curative effect in the relevant part of the missing data will adopt the method of the last observation data before carry forward to supplement.FAS is curative effect evaluation of the main groups.

PPS, per protocol set

The participants meet the inclusion criteria of the requirements of protocal,and complete the whole observation period plan;During the trial there will be no other treatments or drugs affecting the curative effect.PPS is the secondary groups of curative effect evaluation.

SS, safety set

After randomized grouping,participants will use at least one study drugs, and possess all the cases of drug safety evaluation data, which constitute the safety analysis of the present study population.

Statistical analysis method

Step 8.

General principal: The test group and the control group after treatment, compared the main index of the curative effect between group with superiority test, P = 0.05, that is better established. All statistical tests were two-sided test, P = 0.05 can be considered statistically significant difference.

Statistical significance: the main indicators of the incidence of decreased blood pressure, there was a 30% difference between the two groups.

Quantitative data: using arithmetic mean, median, standard deviation and Min and Max for statistical description.

Classification data: frequency, composition ratio or percentage of statistical description.

Efficacy evaluation: The data obtained from the screening period were defined as baseline data for the evaluation of the efficacy. Baseline evaluation by FAS and PPS. Comparisons between groups were performed using rank sum test. The comparison between the measured data was analyzed by one-way ANOVA or rank sum test. P is less than or equal to 0.05 that the excellent effect was established.

Safety evaluation:

① The number, type and severity of adverse events were calculated for each treatment group.

②MH- chi square test or Fisher 's exact probability method was used to compare the incidence of adverse events between the four groups.

③ Single factor analysis of variance to compare four groups of variables in the laboratory test indicators.

④ Statistical description of the three groups after treatment of laboratory indicators positive and abnormal changes in the proportion of.

Trial management

Step 9.

State

This trial will strictly abide by the program and regulations.

The ethical part

Following the Helsinki declaration (2000 Edition) in accordance with the relevant medical research codes and regulations of China. Prior to the start of the study, the ethics committee approved by the medical research unit will be able to carry out clinical trials. Every patient in this study, the research physicians have a responsibility to written form, to comprehensively introduces the research purpose, procedures and the possible risks. Patients should be informed that they have the right to withdraw from the study at any time. The top must give each patient a written informed consent (the appendix is included in the program), research physician has the responsibility to obtain informed consent before each patient in the study, informed consent in clinical trials should be retained for future reference document.

Original data verification

To directly recorded in the case report form data (i.e. no written or electronic records in advance of data) and consider for the identification of the original data, according to the plan in advance to make provision in the monitoring plan clearly stated, otherwise regarded as lack of original data.

Researchers must properly handle all data obtained during clinical studies to ensure the rights and privacy of the participants in the clinical study. Researchers must agree with the arbitrator / Inspector / inspector of clinical research data needed for inspection and audit, in order to verify the accuracy of original data and understand the research progress. If not the original record is verified, researchers should agree to assist the arbitrator / Inspector / inspectors of the quality of the data for further confirmation.

Quality control and assurance

This study is a prospective, randomized, double blind trial, the experimental study design, implementation of the program by the person in charge, I do not participate in data analysis, to avoid the interference of human factors test results.

Informed consent / data protection protocol

It is the responsibility of the investigator to explain the purpose, methodology, benefits and potential risks of this clinical trial for each subject, and to obtain informed consent from the subjects in the clinical trial. Informed consent must be obtained prior to the start of any operational procedures related to clinical trials. For those who are unable to sign their own informed consent for any reason, it is necessary to sign an informed consent form. By signing the informed consent, participants must also agree to allow clinical research associate / Inspector / Health Survey Organization for verification has been obtained on clinical research of the original data and the reliability of data in order to determine the clinical results.

References

Step 10.

[1] 中国消化内镜诊疗镇静"麻醉的专家共识, 临床麻醉学杂志, 09 (2014) 920-927.

[2] O.H. Salman, A controlled, double blind, study of adding Nalbuphine to Propofol for laryngeal mask insertion conditions and hemodynamics in adults, Egyptian Journal of Anaesthesia, 31 (2015) 277-281.

[3] E.V.G. R. FOURNIER, M.MACKSAY and Z. GAMULIN, Onset and offset of intrathecal morphine versus nalbuphine for postoperative pain relief after total hip replacement, Acta anaesthesiologica Scandinavica, 44 (2000) 940-945.

[4] 俞阳, 门诊手术麻醉药的选择, 国外医学.麻醉学与复苏分册, (1992) 319.

[5] 蔡立婧, 张俊, 彭文兴, 朱荣华, 王秀梅, 阳剑, 张啟智, 纳布啡注射液在健康受试者中的药代动力学研究, 中国药学杂志, (2011) 1597-1600.

[6] 黎环, 地佐辛、吗啡、纳布啡对于门诊患者术后镇痛效果的比较, 中国医院药学杂志, (2013) 978-981.

[7] M.Z. Anna Kubica-Cielińska, The use of nalbuphine in paediatric anaesthesia, Anaesthesiology Intensive Therapy, 47 (2015) 252-256.