Rationale and design of influence of volatile anesthesia versus total intravenous anesthesia on chronic postsurgical pain after cardiac surgery using Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials criteria assessment: study protocol for a prospective randomized controlled trial

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Study protocol

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Abstract

Background Many patients develop chronic postsurgical pain (CPSP) after cardiac surgery, which interferes with sleep, mood and quality of life. Studies have suggested that propofol improved postoperative analgesia compared with volatile anesthetics, but the prevention effect on CPSP following cardiac surgery is still unknown. This study has been designed to compare the incidence in CPSP following cardiac surgery receiving volatile anesthesia compared to propofol-based total intravenous anesthesia (TIVA) using Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) criteria assessment. Methods This is a prospective randomized controlled trial. Five hundred adult patients undergoing cardiac surgery will be randomly allocated to the volatile or the TIVA group. The volatile group will receive sevoflurane or desflurane during surgery to provide general anesthesia. The TIVA group will receive propofol-based intravenous agents and no volatile agents during surgery. The primary outcome will be the frequency of CPSP at 3 months, 6 months and 1 year after surgery. CPSP is defined as two ways: sternal and/or thoracic pain: (1) numeric rating scale, NRS >0; (2) meets all six IMMPACT criteria for CPSP assessed using validated pain instruments. Discussion To our knowledge, this is the first prospective randomized protocol investigating the prevention of CPSP following cardiac surgery receiving volatile anesthesia compared to propofol-based TIVA using validated pain instruments in accordance with the IMMPACT recommendations. This study will provide important information on whether the choice of these two anesthetic regimens might influence CPSP after cardiac surgery. Trial registration: Chictr.org.cn, ID ChiCTR1900020747. Registered on 16 January 2019.

Background

Cardiac surgery remains one of the most common forms of major surgery, with over 2 million patients undergoing this procedure worldwide each year[1]. Many patients develop chronic postsurgical pain (CPSP) which persists in the anterior thorax after median sternotomy[1]. It is estimated that CPSP with an incidence of 11%-56% in accordance with different populations and length of follow-up in patients undergoing cardiac or thoracic surgery[2-5]. CPSP that persists after cardiac surgery is a major clinical problem, because it disturbs daily life and interferes with sleep, mood and quality of life[6-8]. Considering the large number of patients who undergo cardiac surgery, identifying potential treatment of CPSP is important[9]. Besides standard postoperative analgesics, the use of corticosteroids, N-methyl-D-aspartate (NMDA) antagonists, alpha-2 agonists, local anesthetics and gabapentinoids are all suggested to reduce the risk for CPSP after cardiac surgery[5]. However, no specific therapy is verified to protect against CPSP[10-12].

Patients undergoing cardiac surgery need general anesthesia with either intravenous anesthetics such as propofol or volatile anesthetics (isoflurane, sevoflurane, or desflurane). Studies have found that propofol, has anti-inflammatory and antioxidative effects on the bio-syntheses of cytokines which play important roles in pain signaling[13]. Besides, propofol's free radical scavenging ability is useful and important for its anti-oxidant properties, and may also play a role in dynamic protection in the body[14]. Moreover, propofol can modulate NMDA receptors in neurons in vivo, which play a crucial role in the transmission

and maintenance of the pain signaling pathway[14, 15]. These anti-inflammatory, free radical scavenging and NMDA receptor antagonistic properties of propofol imply a possible perioperative analgesic effect. The meta-analysis reported by Qiu et al. and Peng et al. suggested that propofol improved postoperative analgesia compared with inhalational anesthesia[16],[17]. However, most previous studies were not designed to detect differences in chronic pain[16, 17], and a few of clinical trials investigating CPSP focused on non-cardiac surgery[18, 19]. To date, no clinical trial has been published focusing on volatile anesthesia versus propofol-based total intravenous anesthesia (TIVA) 's effects on the prevention of CPSP after cardiac surgery through sternotomy.

Prior studies focusing on CPSP in both cardiac and non-cardiac surgery assessed pain using a yes or no scoring system or the numerical rating scale (NRS) valuing the level of pain, and seldom of them used the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations to evaluate CPSP[20]. IMMPACT recommendations for assessment of CPSP evaluate the pain qualities, the level of pain at rest and with movement, the clinical meaningfulness of the pain and the influence of pain on physical and emotional functioning, instead of only focusing on the absence or presence of pain[20-23]. From the above, the aim of this randomized clinical trial is to assess the prevention of CPSP following cardiac surgery through sternotomy receiving volatile anesthesia compared to propofol-based TIVA using validated pain instruments in accordance with the IMMPACT recommendations.

Results

Study design, approval, and registration

The planned study is a parallel group, randomized controlled trial with 1:1 allocation ratio undertaken in West China Hospital of Sichuan University. The trial design and schedule of investigations are summarized in Figure 1. Study recruitment will commence in February 2019. The schedule of enrollments and assessments is as in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure (Additional file 1 and 2). The study has been approved by the Ethics Committee of West China Hospital of Sichuan University and has been prospectively registered at Chictr.org.cn (ID ChiCTR1900020747).

Study aim

The aim of our study is to compare the incidence in CPSP following cardiac surgery receiving volatile anesthesia compared to propofol-based TIVA using IMMPACT criteria assessment.

Participants

We plan to enroll 500 participants age more than 18 years undergoing cardiopulmonary bypass (CPB) for any elective cardiac surgical procedure via a median sternotomy, such as valve, coronary artery bypass

graft (CABG), aorta, or combined procedures. The inclusion and exclusion criteria are presented in Table 1.

Randomization, allocation and concealment

Once informed consent is received and the preoperative assessments completed, patients will enter into the trial. Subjects will be allocated according to a web-based centralized dynamic randomization service. The dynamic randomization is determined by patient characteristics including age, gender, European System for Cardiac Operative Risk Evaluation (EuroSCORE) score, predicted CPB time and body mass index (BMI). Anesthesiologists will be aware of patients' group allocation because they will provide the trial treatment intervention, but they will not be involved in postoperative treatment and investigation. Patients, intensive care physicians, data collectors, and outcome adjudicators are blinded to treatment allocation.

Interventions

Patients who meet the enrollment criteria will be randomized 1:1 to either the volatile or the TIVA group. Three investigators (Hong Yu, Jian-Qiao Zheng and Yu-Si Hua) will explain the treatment intervention in detail and supervise the compliance of intervention throughout the entire procedure (from maintenance of anesthesia to transport to ICU).

The volatile group

The volatile group will receive sevoflurane or desflurane during surgery (from maintenance of anesthesia to transport to ICU and including CPB) to provide general anesthesia. The anesthesia maintenance in the treatment group consists of sevoflurane or desflurane at a minimum end-tidal concentration of 0.5-2 minimal alveolar concentration (MAC) throughout the entire procedure. During CPB, patients will receive sevoflurane or desflurane from a vaporizer connected to an air blender, which is connected to an oxygenator. The MAC is measured at the outlet of the oxygenator of the extracorporeal circulation.

The TIVA group

The TIVA group will receive propofol at an infusion rate of 3-8 $mg \cdot kg^{-1}h^{-1}$ with or without other intravenous agents, and the only absolute criterion for this group is that no volatile anesthetic is used at any time during the procedure.

Perioperative management

Anesthesia induction

General anesthesia will be induced with midazolam, sufentanil, and propofol as necessary. Tracheal intubation will be facilitated with either rocuronium or cisatracurium. The anesthetics type and dosage will not be intervened.

Ventilation setting

Patients will be ventilated using lung protective ventilation strategy before and after CPB. Settings are as follows: pressure-controlled ventilation to maintain a tidal volume of 6-8 $ml \cdot kg^{-1}$ ideal body weight (IBW), a positive end expiratory pressure (PEEP) of 5-8 cmH_2O; an inspiratory to expiratory ratio (I:E) of 1:2; an inspired oxygen fraction of 0.4 to 0.8; and respiratory rate of 10-16/min, adjusted to keep a desired $EtCO_2$ of 35-45 mmHg. A recruitment maneuver with peak airway pressure 30 cmH_2O for 30s, as an essential part of protective ventilation strategy, will be performed before beginning and discontinue of CPB and exiting from operating room. Ventilation or not during CPB will be decided by anesthesia care providers.

Anesthesia maintenance

Propofol or inhalation anesthetics, sufentanil, and nondepolarizing muscle relaxant will be used for maintenance of general anesthesia with dosages at the discretion of the attending clinicians. Sufentanil will be administered to avoid changes of mean arterial pressure (MAP) within 20% from baseline but not less than 65 mmHg and a vasopressor will be administered as necessary. Remifentanil will be administered as an infusion rate of 0.1-0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The dosage of dexmedetomidine will be limited to less than 0.5ug/kg/h if needed. No antiemetic will be administrated for nausea and vomiting prophylaxis.

Postoperative analgesia

After the surgery, patients will be transferred to the intensive care unit (ICU) for further care. Patients will receive an infusion rate of 10-25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine or intravenous (IV) meperidine 100mg to maintain the NRS of less than 4 (0 = no pain, 10 = worst pain imaginable) as assessed by the nursing personnel. IV analgesia will be discontinued and patients will be given oral celecoxib or ibuprofen when the patient is able to tolerate oral medications. No patient-controlled IV analgesia pump will be used for all patients.

Data collection

Baseline characteristics of patients

Demographic data, cardiac history, coexisting medical conditions, comorbidities, smoking status, EuroSCORE score, depression or anxiety history, chronic pain at presentation in an area other than the operative site, surgical procedure, intraoperative sufentanil and remifentanil dosage, and health-related quality of life measured with quality of recovery (QoR)-15 questionnaire[24] will be recorded.

Acute pain assessment at the 24, 48 and 72 hours after surgery

Patients will be visited and evaluated over the first 72 hours after surgery. Pain was assessed on an 11-point NRS scale (0 = no pain, 10 = worst pain imaginable) at 24, 48 and 72 hours after surgery. The amount of opioid analgesics consumed is verified via the electronic medical record and is converted to an equivalent dose of IV morphine[25].

Follow-up at three, six months and at one year

All patients will receive three follow-up phone calls at three, six months and at one year after surgery to answer questions regarding the presence, quality, and severity of pain using the Brief Pain Inventory (BPI) [26], the McGill short form questionnaire[27], and QoR-15 questionnaire[24]. Each patient will leave at least 3 phone numbers and receive a maximum of 3 telephone calls if contact could not be made.

Outcomes

The primary outcome

The primary outcome is the frequency of CPSP at 3 months, 6 months and 1 year after surgery. Chronic thoracic pain is defined as two ways: (1) sternal and/or thoracic pain (NRS >0) which the patient identified as related to surgery; (2) sternal and/or thoracic pain assessed using validated pain instruments in accordance with the IMMPACT recommendations which meet all six IMMPACT criteria for CPSP[28].

IMMPACT Questionnaires

Chronic pain is assessed in accordance with the IMMPACT recommendations in the following six domains[28]: (1) absence or presence of pain in the area of the surgery, (2) clinically important daily average pain (NRS score of $\geq$ 4 on a 0-to10-point scale), (3) clinically important pain at rest (NRS score of $\geq$ 4), (4) clinically important pain intensity upon movement or activity (NRS score of $\geq$ 4), (5) pain qualities, and (6) physical and emotional functioning[21, 22, 29]. The BPI is used to determine the domains 1 to 4 and 6 which measures the pain intensity upon daily average pain, at rest, movement or activity as well as physical and emotional functioning[26]. The McGill Pain Questionnaire is used to assess domain 5 which determines pain quality outcome measures impacting both the sensory and affective pain[27] and a total pain index score of $\geq$ 12 is associated with chronic pain[30]. Subjects have to meet all 6 outcome domains to fulfill the IMMPACT criteria.

The secondary outcomes

The secondary outcomes focus on: (1) NRS pain scores (0-10) 24, 48 and 72 hours after surgery, (2) opioid consumption during the first 72 hours after surgery, (3) the BPI, McGill pain questionnaire, and health-related quality of life measured with QoR-15 at 3 months, 6 months and 1 year after surgery.

Statistics

Sample size estimate

The sample selected for this study was based on the finding of our prior study exploring the incidence and possible risk factors of the CPSP in patients undergoing cardiac surgery with CPB via median sternotomy which showed that the CPSP at postoperative 3 months occurred in 60.9% patients[31]. The sample size for the study is 250 patients per group, for a total of 500 patients. The study has 80-90%

power to detect a 25 relative risk reduction for the primary outcome of CPSP at 3 months at a significance level (alpha) of 0.05 (two-sided), anticipating a 50-60% CPSP rate in the control (inhalation or TIVA) arm with allowance of 10% of patients lost to follow-up or withdraw from the study.

Statistical analyses

Data will be expressed as mean ± standard deviation (SD) or number (percentage). Baseline characteristics will be compared using the Chi-square or Fisher exact tests, Student t test, or nonparametric test as appropriate. The primary outcome, the occurrence of CPSP at 3, 6 months and 1 year after surgery will be compared using Chi-square or Fisher exact tests, and the relative risks and their 95% confidence interval (CI) will be calculated. All analyses of primary outcomes will be conducted using the intent to treat approach and a sensitivity analysis of per-protocol approach will also be performed. In addition, multiple logistic regression analysis will be used to identify relevant baseline covariates associated with the primary outcome. Variables tested in the model will be selected if the P value was less than 0.10 or if they are clinically relevant (such as analgesics usage during surgery). All secondary outcomes are continuous variables and will be compared using the unequal-variance student t test. Results were considered statistically significant at a P value less than 0.05. Statistical analyses are performed using statistical software SPSS 17.0.

Participant timeline

Patients recruitment and data collection will be started in February 2019, and until sufficient participants (500 patients) are enrolled, which is scheduled at the end of June 2019. One-year postoperative follow-up will be completed in June 2020.

Data management and monitoring

All original data will be recorded in the Case Report Forms accordingly. The study supervisor (Hai Yu) will supervise the trial conduction every month.

Discussion

To our knowledge, this is the first prospective randomized protocol investigating the prevention of CPSP following cardiac surgery through sternotomy receiving volatile anesthesia compared to propofol-based TIVA using validated pain instruments in accordance with the IMMPACT recommendations.

CPSP is defined as persistent or recurrent pain lasting longer than 3 months, and without apparent cause[32]. Our results are clinically important because the incidence of CPSP has been considered to occur in up to 11-56% of patients undergoing cardiac or thoracic surgery with median sternotomy, with no established methods of prevention currently established[10-12]. As we know, general anesthesia is routinely used in cardiac surgery. To date, propofol is well established to improve postoperative analgesia compared with inhalational anesthesia[16][17]. As acute pain is viewed as an initial phase of pain responses that has the potential to progress to chronic pain[5], even if the role is conflicting, propofol was

assumed to have the potential to prevent CPSP. Ogurlu et al. reported that general anesthesia with propofol was associated with reduced persistent pain at three months, compared to sevoflurane-based anesthesia, among patients undergoing open abdominal hysterectomy[18]. Besides, Song et al. found consistent results in patients scheduled for thoracotomy during surgery for lung and esophageal cancer[19].

However, there is no information about the type of anesthesia and chronic pain in cardiac surgery. To date, no clinical trial has been published focusing on the effect of volatile anesthesia versus propofol-based TIVA on postoperative acute and chronic pain after cardiac surgery through sternotomy.

On the other hand, prior studies focusing on CPSP in both cardiac and non-cardiac surgery assessed pain using a yes or no scoring system or the NRS valuing the intensity of pain, and seldom of them used the IMMPACT recommendations[20]. IMMPACT is a consortium of researchers and practitioners in pain medicine whose mission is to develop consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain[33]. Assessing the domains of pain recommended by IMMPACT, it would show the diversified effect of anesthetics on pain at rest, pain with activity, pain qualities, or the physical or emotional impact of the pain.

In summary, this study will be an important randomized study to provide information on whether the choice of these two anesthetic regimens might influence CPSP after cardiac surgery. Moreover, results on CPSP using validated pain instruments in accordance with the IMMPACT recommendations will add to currently available data on the CPSP, which really has clinical meaningfulness and disturbs patients' physical and emotional functioning and quality of life.

Abbreviations

CPSP, chronic postsurgical pain; NMDA, N- methyl-D-aspartate; TIVA, total intravenous anesthesia; NRS, numerical rating scale; IMMPACT, Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; CPB, cardiopulmonary bypass; CABG, coronary artery bypass graft; EuroSCORE, European System for Cardiac Operative Risk Evaluation; BMI, body mass index; MAC, minimal alveolar concentration; IBM, ideal body weight; PEEP, positive end expiratory pressure; I:E, inspiratory to expiratory ratio; MAP, mean arterial pressure; ICU, intensive care unit; IV, intravenous; QoR, quality of recovery; BPI, Brief Pain Inventory.

Declarations

Ethical Approval and Consent to participate

The study protocol has been approved by the Ethics Committee of West China Hospital of Sichuan University (first version protocol approved on 16 January 2019 with number 2018[562]). We will obtain informed consent from patients when recruiting before the experiment. The consent obtained from participants will be written. The patients can withdraw from the trial at any time.

Trial status

The protocol version is 1.0 (issue date: 1 January 2018). Patients recruitment and data collection will be started in February 2019, and until sufficient participants (500 patients) are enrolled, which is scheduled at the end of June 2019. One-year postoperative follow-up will be completed in June 2020.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

Conceptualization by Hai Yu (HY1); Data curation by YSH; Formal analysis by YSH; Funding acquisition by HY1 and Hong Yu (HY2); Investigation by HY2, YSH, JQZ and SFR; Methodology by HY1 and HY2; Project administration by HY1 and HY2; Resources by HY1; Software by SFR; Supervision by HY1; Validation by HY2, JQZ, YSH; Visualization by JQZ,YSH; Writing-original draft by HY2; Writing-review & editing by HY1. All authors read and approved the final version of the manuscript and ensure this is the case.

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Tables

Table 1. Inclusion and exclusion criteria.

Included criteria	Excluded criteria
1. age older than 18 years	1. combined cardiac and non-cardiac surgery
2. received cardiopulmonary bypass for cardiac surgery via a median sternotomy	2. emergency surgery
3. signed the informed consent form	3. pregnancy
	4. suspected family history of malignant hyperthermia or propofol infusion syndrome
	5. failed to cooperate with follow-up because of disturbance of comprehension

Additional Files

Additional file 1: The SPIRIT 2013 checklist of this trial.

Additional file 2: The SPIRIT Figure of this trial.

Figures

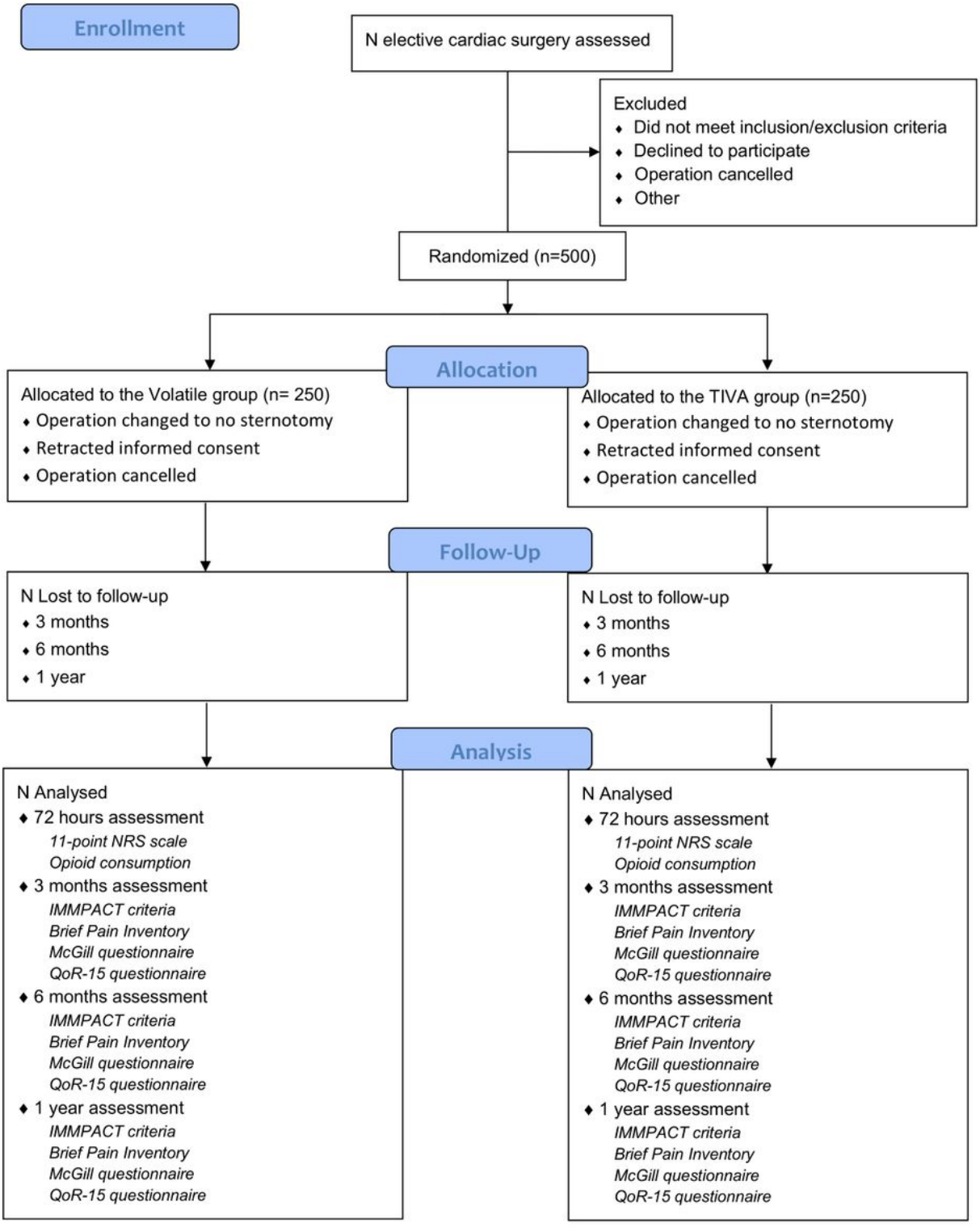

Figure 1

Consort diagram of study participant flow. TIVA, total intravenous anesthesia; NRS, numeric rating scale; IMMPACT, Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; QoR-15, quality of recovery-15.

Supplementary Files

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

- Additionalfile1SPIRIT2013ChecklistCPSP.pdf
- Appendix2SPIRITFigure.pdf