Supplementary Material

Evaluation of the effect of new multimodal analgesia regimen for cardiac surgery: a prospective, randomized controlled, single-center clinical study

Research Protocol

Inclusion criteria:

1) Patients aged 18 to 80 years who will undergo elective sternotomy with cardiopulmonary bypass cardiac surgery;
2) ASA GradeII-III;
3) Body mass index (BMI) 18~31;
4) Voluntary participation and signed informed consent.

Exclusion criteria:

1) Unwilling to join the study or unable to communicate;
2) Minimally invasive cardiac surgery;
3) People with liver and kidney dysfunction;
4) People with uncontrolled diabetes;
5) People with sleep apnea;
6) Known history of alcohol, drugs or narcotics abuse.

Exit criteria:

1) Re-operation due to surgical reasons;
2) The patient withdrew informed consent.

Methods

Patients will be approached for consent on the day before surgery. After obtaining informed consent, the patients will be randomized utilizing sequentially numbered opaque sealed envelopes to one of two groups (ratio 1:1) by the study co-ordinator: traditional group (group T) and multimodal analgesia group (group M).

Anesthetic management

Same anesthetic protocol will be used in both groups.

All patients in both groups will have routine fasting and water-deprivation before surgery. After the patients entered the operating room, central venous, radial artery and urinary catheters will be inserted. The ECG and radial artery pressure will be monitored.

The anesthesia induction and maintenance plan is as follows: anesthesia will be induced by midazolam 2mg, propofol target effect-site concentration 1~3μg/ml, sufentanil 0.2~0.5μg/kg, and rocuronium 0.9~1.2mg/kg. After tracheal intubation, sevoflurane 0.6~1MAC and propofol target effect-site concentration 1~3μg/ml will be used to maintain anesthesia. During the surgery, the attending anesthetist will determine the dose and timing of sufentanil 0.1~0.2μg/kg pro re nata (prn) and rocuronium 0.2~0.4mg/kg prn based on the procedure, operation progress, hemodynamic parameters, muscle relaxation, and adjust the dosage of sevoflurane and propofol to maintain BIS at 40~60.

Both groups of patients will receive same PONV prophylaxis regimen.

- Tropisetron: 6mg IV 30 min before the end of the surgery;
- Dexamethasone: 4mg IV 30 min before the end of the surgery.

After surgery, all patients will be transferred to ICU for recovery and will be received conventional sedatives in ICU until initiation of the extubation procedure. Patient will be extubated when meeting extubation criteria. Indications for extubation: recovery of consciousness; active cough and swallowing reflex; residual effects of muscle relaxants have been reversed; adequate spontaneous breathing rate, sufficient tidal volume; normal arterial blood gas analysis; stable circulatory function, heart rhythm, and urine output; bleeding controlled. If extubation fails, conventional sedatives will be administered continuously in ICU.

Patient controlled intravenous analgesia (PCIA) pump (1 μg/ml sufentanil, background 0 ml/h, blous 4 ml, lock-in time 10 min) will be used after tracheal extubation until 72h after surgery. Education on using PCIA pumps will be provided during preoperative visit and after tracheal extubation. If pain cannot be relieved after 3 consecutive blous, or the patient cannot tolerate the side effects of the PCIA, rescue analgesia will be provided by the on call physicians.

Study protocol

For group M, patients will receive treatment as following:

Pre-operative:

- Gabapentin: 300 mg (reduce to 100 mg for those >65 years old) oral administration (per os, p.o)1 hour before surgery;
- Acetaminophen: 500 mg p.o 1 hour before surgery;
- No preoperative medication for group T.

Intraoperative:

- Ketamine: 0.5 mg/kg with induction bolus, followed by 5μg/kg/min infusion until the initiation of the extubation procedure (maximum total dose 3 mg/kg);
- Lidocaine: 2mg/min infusion after anesthesia induction, and be continued until the initiation of the extubation procedure;
- Dexmedetomide: 0.4 μg/kg/h infusion after anesthesia induction, and be continued until the initiation of the extubation procedure.

Postoperative:

- Ketamine: 5μg/kg/min infusion (maximum total dose 3 mg/kg) in ICU until the initiation of the extubation procedure;
- Lidocaine: 2mg/min infusion in ICU until the initiation of the extubation procedure;
- Dexmedetomide: 0.4 μg/kg/h infusion in ICU until the initiation of the extubation procedure.
- Gabapentin: 300 mg (reduce to 100 mg for those >65 years old) oral administration p.o three times a day (ter in die, tid) starting extubation until discharge;
- Acetaminophen: 500 mg p.o tid starting extubation until discharge.

Evaluation of outcomes

Pain will be assessed by the visual analog scale (VAS). Patients will be followed up twice a day (7am-9am and 7pm-9pm) to record the VAS at rest and on coughing until discharge. The maximum VAS within the certain time period will be recorded. VAS ≥ 4 is used as a criterion for poor analgesia and defined as moderate to severe pain. The incidences of daily moderate to severe pain are defined as the proportion of patients with daily VAS score ≥ 4 at least once in each group. The incidence of moderate to severe pain during hospitalization is defined as the proportion of patients with VAS score ≥ 4 at least once during hospitalization in each group.

The amounts of intraoperative, postoperative and total dosage of sufentanil will be recorded.

Venous blood samples will be collected preoperative, on the first, second and third morning after surgery to measure blood glucose and complete blood count. Systemic inflammatory indexes (including Neutrophil/Lymphocyte ratio, NLR; Platelet/Lymphocyte ratio, PLR; Lymphocyte/Monocyte Ratio, LMR and Systemic Immune-inflammation Index, SII) will be calculated from the complete blood count.

The mechanical ventilation time, length of ICU stay, length of hospital stay will be recorded for both groups.

Remedial analgesia, PONV, dizziness, acute kidney injury (hemodialysis) and other complications will be assessed twice a day (7am-9am and 7pm-9pm) until discharge.

The patients will be followed up by telephone to assess the chronic pain at 3 months and 1 year after surgery.

Primary outcome

The incidences of moderate to severe pain on coughing during hospitalization.

Secondary outcomes

1) The incidences of moderate to severe pain at at resting and on coughing at the first, second and third postoperative day and at discharged;
2) The incidences of moderate to severe pain at at resting states during hospitalization;
3) Intraoperative, postoperative and total sufentanil consumption;
4) The incidences of rescue analgesia;
5) The incidences of PONV;
6) The incidences of dizziness;
7) Blood glucose at preoperative, the first, second and third morning after surgery;
8) NLR, PLR, LMR and SII at preoperative, the first, second and third morning after surgery;
9) Mechanical ventilation time (hrs), ICU stay (days), hospital stay(days);
10) The incidences of acute kidney injury (hemodialysis);
11) The incidences of other complications;
12) The incidences of chronic pain.

Implementation of blind method

- The patients will not know the randomization allocations;
- The attending anesthesiologists (investigators), who participate in preoperative and intraoperative care, will not be blinded and will not participate in the follow-up or outcomes evaluation;
- The staffs, who responsible for follow-up and evaluation of study outcomes, will be blinded;
- The other participants will not know the random results.

Statistical analysis

Sample size was calculated, based on previous data from our acute pain service in the same hospital before the start of this trial. Assuming the incidence of moderate to severe pain in group T at 64%, and group M at 35%, with a power of 80% and significance level of 5%, each group need 43 patients. Therefore, 54 patients are planned in each group to account for potential dropouts.

Count data will be expressed as the frequency (percentage), and the chi-square test or Fischer's exact test will be used for comparison between groups, and the two-sided significance value will be evaluated.

Measurement data will be expressed as the mean (95% confidence interval) for continuous variable and the median (interquartile range) for discrete variable. Two sets of sample t-tests will be used for the comparison of normal distribution data, and the Wilcoxon rank-sum test will be used for non-normal distribution data. $P<0.05$ is defined as statistically significant difference. All statistical analyses will be performed using SPSS 20.0.