

Comparing the Effects of Dexmedetomidine versus Propofol on the Treatment of Emergence Agitation in Adults after General Anesthesia: study protocol for a randomized controlled trial (DP-TEA Trial)

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Study protocol

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Abstract

Background

Emergence agitation (EA) from general anesthesia is a common complication in the post anesthesia care unit (PACU). Once EA happens, there is still no guidelines established to recommend the medication administration in adults. Propofol is widely used in managing agitated patient in the PACU, but it is lack of analgesia and can suppress breathing transiently. Intraoperative infusion of dexmedetomidine is proved to have preventive effect on EA, but the treatment effect of dexmedetomidine on EA occurring in the PACU remains unknown. This study aims to compare the effects between dexmedetomidine and propofol on relieving emergence agitation in the PACU in adult patients after general anesthesia.

Methods

In this randomized, controlled, single-blinded clinical study, a total of 120 adult patients aged 18-65 years of both genders, with American Society of Anesthesiologists (ASA) classification I or II who develop emergence agitation in the PACU after general anesthesia will be included. Patients will be randomized at 1:1 ratio to two groups, receiving either a single dose of dexmedetomidine (0.7ug/kg) or propofol (0.5mg/kg). The primary outcome is the recurrence rate of EA assessed by the Riker Sedation-Agitation Scale (RSAS). The secondary outcomes are RSAS scores and vital signs before and after intervention, the consumption of sufentanil in the PACU, nausea and vomiting scores evaluated by a four-point postoperative nausea and vomiting (PONV) scale when leaving the PACU, duration in the PACU, adverse events (desaturation, severe bradycardia, shivering, dizziness, laryngospasm, severe coughing, reintubation) and recovering quality evaluated by the 40-item quality of recovery scale (Qo-R 40).

Discussion

Previous studies are almost about the efficacy of premedication on preventing EA, while medicine administration on treating EA is reported rarely. This study is designed to investigate whether a single dose of dexmedetomidine can relieve EA more efficiently and improve recovery quality of adult patients form general anesthesia more significantly comparing to propofol.

Trial registration

ClinicalTrials.gov ID: NCT04142840. Registered on October 26, 2019.

<https://clinicaltrials.gov/ct2/show/NCT04142840>.

Introduction

Emergence agitation (EA) from general anesthesia is a common complication in the post-anesthesia care unit (PACU), with an incidence ranging from 4.7% to 74% in adult patients undergoing various surgical procedures(1-6). An agitated patient may remove the endotracheal tube, oxygen mask, catheters or wound packing, leading to serious sequences such as hypoxia and hemorrhage. Furthermore, seriously

agitated patients can pose an immediate harm to care-providers(7). Despite the high prevalence and serious sequelae, the underlying mechanism of EA remains to be elusive. Several risk factors including premedication benzodiazepines, pain, long duration of surgery, breast and abdominal surgery, presence of a tracheal tube and/or a urinary catheter, and preoperative anxiety have been identified to be account for this phenomenon(2-4, 8).

In the past few years, anesthesiologists have been striving to reduce the incidence of EA and improve the quality of patient's postoperative condition with the help of various drugs and techniques. Several drugs such as remifentanyl(9), magnesium sulphate(5) and dexmedetomidine(1, 10, 11) have been suggested as potential prophylactic interventions of EA in adult patients. However, little progress has been made in therapeutics. According to our clinical experience, EA is still difficult to manage once happens.

Nowadays, propofol is the most currently used drug in managing agitated patient in the PACU, but it is lack of analgesia and can suppress breathing transiently(12). Dexmedetomidine is a highly selective α_2 -receptor agonist and has sympatholytic, analgesic and sedative properties without causing respiratory depression at the clinically approved dosage(13). Previous studies have shown the preventive effect of perioperative infusion of dexmedetomidine on EA, especially in pediatric patients. However, the treatment effect of dexmedetomidine on EA occurring in the PACU remains unknown.

In this randomized study, we aim to compare the effects between dexmedetomidine and propofol on relieving EA in the PACU in adult patients after general anesthesia. Furthermore, we evaluate the effects of dexmedetomidine on the patient's quality of recovery.

Objectives

The primary objective is to compare the effects of dexmedetomidine versus propofol on treating EA according to the recurrence rate of EA 15 min after intervention.

The secondary objectives include:

1. Comparing the sedative outcomes after intervention between the two arms;
2. Investigating the safety and tolerability of a single dose of 0.7ug/kg dexmedetomidine by monitoring vital signs;
3. Comparing the effects of the two drugs on postoperative nausea and vomiting (PONV), postoperative pain, and duration in the PACU;
4. Evaluating the recovery quality between the two groups after 24 hours.

Methods

Study design and setting

This study is a randomized, controlled, single-blinded clinical trial, which is designed in accordance with the SPIRIT 2013 Checklist: recommended items to address in a clinical trial protocol (Additional file 1). The final study version 2.0 was approved by the Ethics committee of Renji Hospital affiliated to Shanghai Jiao Tong University School of Medicine (Ethical document is affiliated as Additional file 2) and registered in [clinicaltrials.gov](https://www.clinicaltrials.gov). (NCT04142840). A patient will be screened before the surgery day to make sure the potential eligibility for this research. Timepoints of enrolment and assessments are shown in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure (Figure.1). The study will be conducted in Renji Hospital affiliated to Shanghai Jiao Tong University School of Medicine from October 2019 to October 2021, where 40 to 50 thousand surgeries under general anesthesia are performed every year.

Consent

Due to their confusion and inability to lay down new memories, it is not possible to obtain signed consent from patients in EA, and obtaining prospective consent might lead to harmful delays to the initiation of treatment. Therefore, we will get verbal consent at the time of enrolment with written consent taken as soon as possible after trial participation. More specifically, firstly, patients scheduled to undergo elective surgery will be screened before the surgery day to make sure the potential eligibility for this research. During our preoperative anesthesia visit, the procedures involved in the study, and the possible assignment will be explained. Then, verbal consent from the patients or their legally authorized representatives will be gained by study staff in the presence of an independent witness. Secondly, once EA happens, the patients will be randomly assigned into one of the two study groups to receive treatment immediately. Then full written informed consents will be sought later from the patients or their legally authorized representatives as soon as possible.

Eligibility criteria

The inclusion criteria are adult patients aged 18-65 years of both genders, with American Society of Anesthesiologists (ASA) classification I or II, who develop EA after general anesthesia with verbal consent.

The exclusion criterion are as follows:

- age younger than 18 years or older than 65 years;
- ASA classification \geq III;
- preoperative lung dysfunction (including pneumonia, atelectasis, acute respiratory distress syndrome, acute lung injury, and so on);

- preoperative heart dysfunction (including severe cardiac coronary disease, unstable angina, left ventricular ejection fraction $\leq 30\%$, sick sinus syndrome, bradycardia: heart rate (HR) ≤ 50 beats/min, second or third degree atrioventricular block);
- history of mental disease;
- uncontrolled hypertension (baseline: systolic blood pressure (SBP) ≥ 160 mmHg or diastolic blood pressure (DBP) ≥ 110 mmHg);
- cancers;
- enrolled in other researches within 90 days;
- allergic to dexmedetomidine or propofol;
- body mass index (BMI) less than 18 kg/m² or more than 30 kg/m².

Outcomes

Primary outcomes

The primary outcome is the recurrence rate of EA assessed by the Riker Sedation-Agitation Scale (RSAS) (Table 1).

7	Dangerous agitation	Pulling at tracheal tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing from side to side;
6	Very agitated	Does not calm down despite frequent verbal reminders of limits, require physical restraints, biting endotracheal tube;
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down with verbal instructions;
4	Non-agitated	Calm and cooperative;
3	Sedated	Calm, awakens easily, follows commands, difficult to arouse, awakens to verbal stimuli or gentle shaking, but drifts off again, follows simple commands;
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously;
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands;

Secondary outcomes

- the RSAS scores before and after intervention;

- the vital signs before and after intervention, such as HR, mean blood pressure (MBP), peripheral capillary oxygen saturation (SpO₂);
- the consumption of sufentanil in the PACU;
- the PONV scores evaluated by a four-point PONV Scale (Table 2)

0	No nausea
1	Mild nausea
2	Sever nausea requiring antiemetics
3	Retching, vomiting or both

- the duration in the PACU;
- adverse events such as oxygen desaturation (defined as SpO₂<90%, regarded as severe desaturation when SpO₂<85%) and severe bradycardia (defined as HR<50 beats/min), shivering, dizziness, laryngospasm, severe coughing, and reintubation.
- the recovering quality 24 hrs after surgery evaluated by the 40-item quality of recovery scale (QoR-40) (Affiliated as additional file 3).

Randomization

Computer-generated random numbers will be concealed in opaque envelopes. Once EA occurs, the envelope in the PACU will be opened. Based on a 1:1 allocation ratio, the participants will randomly be assigned to dexmedetomidine group (DEX group) or propofol group (PRO group).

Blinding

Considering the different color of the two injections and the safety of patients, an anesthesiologist will open the envelope containing random number and a nurse (follow the prescription) in the PACU is arranged to implement the infusion of either dexmedetomidine or propofol when EA occurs. These unblinded staffs will not be involved in outcome assessment. On the other hand, patients, staff responsible for outcome assessment and data collection and statistician are all blinded to the intervention assignment.

Intervention

Electrocardiogram (ECG), SpO₂, HR and non-invasive blood pressure (NBP) will be monitored once the eligible patient enters into the operating room at 5-min intervals. General anesthesia will be induced with midazolam 0.05mg/kg, propofol 2-2.5mg/kg, sufentanil 0.2-0.5µg/kg, and tracheal intubation will be

facilitated with rocuronium 0.7 mg/kg. After intubation, anesthesia will be maintained with sevoflurane and remifentanyl based on a bispectral index (BIS) target range of 40-60. Neuromuscular blockade will be maintained via rocuronium intermittently. End-tidal carbon dioxide will be controlled between 35mmHg to 45mmHg. Blood pressure will be administrated between 80% and 120% of the baseline by vasoactive agents or adapting anesthesia depth. HR will be maintained between 50-100 beats/min with a single dose of 0.01mg/kg atropine when HR is below 50 beats/min and 0.5mg/kg esmolol when HR is over 100 beats/min.

By consulting the surgeons, all the anesthesia agents are discontinued 5 minutes prior to the end of the surgery, and the patient will be transferred to the PACU. ECG, HR, SpO₂ and NBP are monitored immediately and then measured at 5-minutes intervals. Reversal agents (neostigmine 0.04mg/kg and atropine 0.15mg/kg) are given to antagonize the residual muscular relaxant when patients exhibit spontaneous breathing and a return of two visual twitch responses of the train-of-four (TOF) stimuli. Extubation will be performed when the patient is able to respond to commands and tidal volume is more than 5ml/kg with a regular breathing. EA is defined as when the RSAS score >5, =7 is defined as dangerous agitation(14). Patients will be assessed in the PACU by an attending nurse anesthetists who have received standardized training by the study taskforce members. Patients recover without EA will be ruled out. The flowchart is shown in Figure.2.

[Figure.2: The flowchart of the trial]

Once EA occurs, the RSAS scores of agitated patients will be recorded. Patients assigned to DEX group will be infused with 0.7ug/kg dexmedetomidine and PRO group patients are to be treated with 0.5mg/kg propofol by experienced nurses following the doctors' prescription. Hemodynamic parameters, including HR, MBP and SpO₂ are recorded at 4 time points: immediately arriving at the PACU (baseline, T0); 1 minute (T1) and 15 minutes (T2) after intervention; being discharged from the PACU (T3). Patients will be assessed by the RSAS again 15min after intervention (T2) and whether the second EA occurs or not will be noted. During the PACU stay, postoperative pain will be assessed using an 11-point NRS (15, 16) whenever patients ask for pain medication. If a NRS score is ≥ 5 , additional 5-10 μ g sufentanil will be injected as rescue medication. PONV will be measured by a 4-point PONV scale. When a patient's PONV scale score is ≥ 2 , 4 mg ondansetron will be administrated. The patient will be transferred to the ward once meeting an Aldrete score ≥ 9 (17). In addition, adverse events (oxygen desaturation (defined as SpO₂<90%, regarded as severe desaturation when SpO₂<85%) and severe bradycardia (defined as HR<50 beats/min), shivering, dizziness, laryngospasm, severe coughing, and reintubation) and length of PACU stay will also be recorded.

Twenty-four hours after surgery, the patient will be visited with a QoR-40 scale to be finished. (18). A QoR-40 scale consists of emotional state (9 items), physical comfort (12 items), psychological support (7 items), physical independence (5 items), and pain (7 items). Each item is graded on a five-point score, and global scores range from 40 (extremely poor quality of recovery) to 200 (excellent quality of recovery).

Safety consideration

In our study, both dexmedetomidine and propofol are common anesthetics in clinical anesthesia. A rapid bolus of dexmedetomidine (0.5µg/kg) has been proven to be hemodynamically acceptable in children(19), and propofol with a dose of 0.5mg/kg is a routine usage. To ensure patients' safety, firstly, unblinded researchers will implement the infusion; secondly, rescue medication like vasoactive agents and noninvasive positive pressure ventilators will be prepared; thirdly, participants will be continuously monitored till 24 h after surgery. Adverse events will be timely recorded and treated promptly according to routine practice and should be followed up until it has completely resolved. Severe adverse events (defined as signs and symptoms last even longer, significantly affect daily activity and life, and do not recover after simple treatment) will be reported to the the Ethics committee of Renji Hospital as soon as possible. If the patient's harm level meets the insurance claims, payment will be arranged as soon as possible. If the patient's harm level meets the insurance claims, payment will be arranged as soon as possible.

Data collection and management

Preoperative variables are as follows: demographic characteristics (name, age, sex, height, weight, BMI), diagnosis, scheduled surgery name, ASA classification, laboratory results (liver and kidney function tests, routine blood tests) and an electrocardiogram report. Perioperative data include duration of the surgery, dosage of medications used in induction and maintenance of general anesthesia, fluid input and output. Postoperative parameters include: vital signs (HR, MBP and SpO₂), the RSAS scores, the NRS scores, the PONV scores, the consumption of sufentanil, ondansetron and vasoactive agents, extubation time, adverse events and the duration in the PACU, QoR-40 scale scores in 24 hrs after surgery.

All the data will be recorded into the case report forms (CRF) timely, completely, and correctly. The data will be monitored and sampled regularly by independent auditors from the Renji Hospital Clinical Research Institute and data queries will be answered by investigators. We have no plan in interim analysis until the target sample size is achieved.

Confidentiality

All related information of participants will be kept in a locked file cabinet, which is only available to researchers to ensure that the research is conducted in accordance with the regulations. Members of the government management department or ethics review committee can access to patients' personal data in the research unit as required. When this research result is published, no personal information will be disclosed.

Sample size

The sample size calculation is based on the treatment effects on EA. In previous studies, the efficacy of propofol on EA treatment was 25%. We hypothesize that the efficacy of dexmedetomidine on EA treatment is 50% ($\alpha=0.05$ and a power of 80%), so a sample size of 55 patients is required for each group. Considering a 10% dropout rate, we finally decide to enrol 60 patients per group.

Data analysis

Statistical analysis will be performed using SPSS software (version 24.0; SPSS Inc., IBM, Chicago, IL, USA). Continuous variables (such as age, height, weight, BMI, duration of the surgery and anesthesia, length of PACU stay) will be presented as mean \pm standard deviation (SD) or median (interquartile range) based on normal distribution checked by Kolmogorov-Smirnov test. The differences between groups will be analyzed with independent t-test or Mann–Whitney U test as appropriate. Categorical variables (such as the recurrence rate of EA, the incidence adverse events) will be expressed as number of patient (percentage) and analyzed using Chi-squared test or Fisher's exact test. Repeated-measures data like vital signs will be analyzed by two-way analysis of variance (ANOVA) followed by Bonferroni correction. A two-tailed P value ≤ 0.05 is considered to be statistically significant.

Analysis will be performed on an intention-to-treat (ITT) principle, all participants will be included as being randomized. For primary endpoint (the recurrence rate of EA), a per-protocol (PP) analysis will be also performed.

As all of our endpoints will be identified in the PACU or 24h after surgery, and data recorded on CRF will be double-checked, so a small amount of missing data will be expected in this trial. To accomplish a complete case analysis, multiple imputation will be undertaken in each group separately with a sensitivity analysis for the assumptions performed (i.e. missing completely at random). Full details of the imputation procedure will be reported.

Discussion

Previous studies about EA are mostly concentrated on the preventive medication(1, 4, 11, 20), while little progress has been made in the therapy of EA. Once occurring without immediate and efficient treatment, EA will not only add extra burden to nursing work in the PACU but also bring negative effects to the patients' prognosis. Therefore, it's of great necessity to find a more ideal medicine for the management of EA with as few side effects as possible. Based on the prophylactic role of dexmedetomidine in EA and successful case reports of using dexmedetomidine as rescue therapy(21) for emergence delirium in adults reported previously, we designed this clinical trial to compare dexmedetomidine with propofol, which is a major choice in terms of EA management in China nowadays, to provide the evidence of the

superiority of dexmedetomidine on improving the recovering quality of agitated adult patients after general anesthesia.

One major concern of our trial is that we will seriously control medication during general anesthesia in each arm to promise the minimally residual effects of other medicine except for propofol or dexmedetomidine on resuscitation. However, there are also limitations in our study. Firstly, to promise the patients' safety, our staff can't be blinded to the two medications. But the unblinded staff won't be involved in the assessment and data analysis. Secondly, as a single-center trial, our results may not be applicable to other centers due to possible existing selection bias. Considering that our hospital is a top-level general hospital in China, in which varied types of surgeries of different organ or systems are involved, the selection bias in enrolment can be reduced maximally.

Trial status

The recruitment of this trial was initiated on November 1, 2019 but suspended for 6 months since January 18,2020 due to Covid-19 outbreak in China. We restarted the trial on July 25,2020 and is currently recruiting patients. We expect to complete the study on December 31, 2021.

Protocol version number: DP-TEA 2.0. Date: September 10,2019.

Abbreviations

EA: emergence agitation

PACU: post-anesthesia care unit

ASA: American Society of Anesthesiologists

BMI: body mass index

QoR-40: quality-of-recovery questionnaire

RSAS: Riker Sedation-Agitation Scale

SBP: systolic blood pressure

DBP: diastolic blood pressure

PONV: postoperative nausea and vomiting

NRS: numerical rating scale

MAP: mean blood pressure

BIS: bispectral index

TOF: train-of-four

SpO₂: peripheral oxygen saturation.

Declarations

Affiliations

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Ethics approval and consent to participate

This study has been approved by the Ethics committee of Renji Hospital affiliated to Shanghai Jiao Tong University School of Medicine (last approval 14th, October 2020). The written informed consent will be obtained from the patients or authorized family members.

Protocol amendments

Any important protocol modifications (such as changes to eligibility criteria, outcomes and analyses) will be reviewed by the principal investigator who will sign and date the amendment, which will be submitted to ethics committee for approval later.

Consent for publication

All authors gave their consent for publication.

Dissemination plans

The study results will be shared at professional conferences via oral reports or posters.

Availability of data and materials

The data that support the findings of this study will be available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SZ designed this trial and WY helped with modification and implementation. XY, YZ and JG are the main executors in the PACU, who are responsible for interventions and make sure the safety of patients. XS assesses patients and fills in case report forms. ZF is responsible for integrating data and drafting the first version of this manuscript. All the authors made a significant contribution to this study and approved this final protocol.

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Figures

TIMEPOINT**	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
	-1 day	Surgery day	Surgery day	t ₁	t ₂	t ₃	+1 day
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
<i>Dexmedetomidine group</i>			X				
<i>Propofol group</i>			X				
ASSESSMENTS:							
<i>Clinical characteristics</i>			X				
<i>Vital signs</i>			←—————→				
<i>RASS score</i>				←————→			
<i>Extubation time</i>			X				
<i>Adverse events</i>			X				
<i>The 2nd EA occurs or not</i>			X				
<i>The maximum NRS score</i>			X				
<i>Aldrete score</i>						X	
<i>Medication consumptions</i>						X	
<i>PONV scale score</i>						X	
<i>QoR-40 score</i>							X

Figure 1

The schedule of enrolment, interventions, and assessments. RSAS: Riker Sedation-Agitation Scale; PONV: postoperative nausea and vomiting; NRS: numerical rating scale; QoR-40: quality-of-recovery questionnaire.

The DP-TEA Trial Flow Diagram

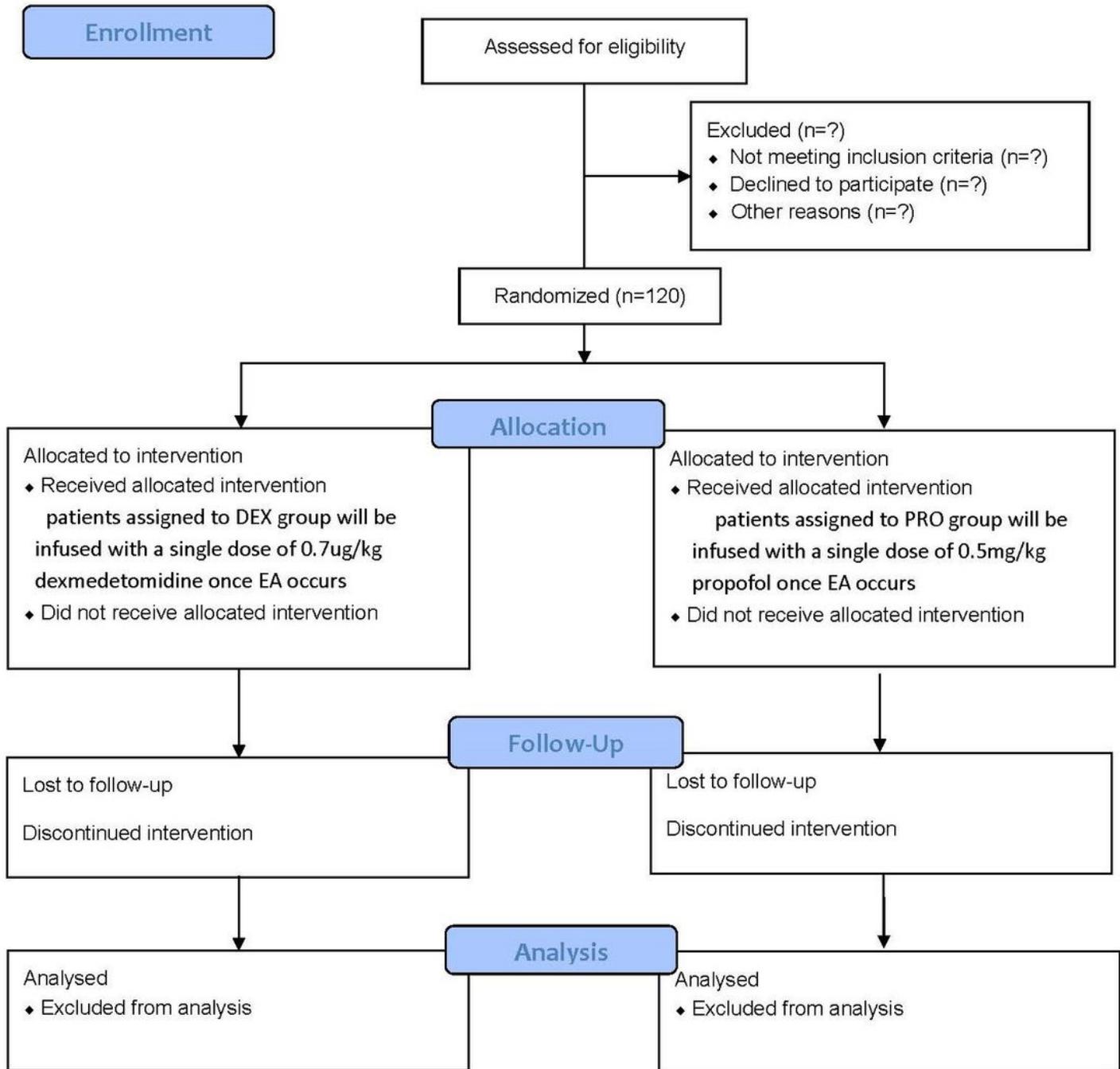


Figure 2

The flowchart of the trial

Supplementary Files

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

- [Additionalfile3QoR40scale.pdf](#)
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