Research Square

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Determination of the 90% effective dose of remimazolam for anesthesia induction in children undergoing ophthalmic procedures: A biased-coin design up-and-down sequential trial

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Research Article

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Abstract

Background

Remimazolam has been used in clinical practice of general anesthesia and sedation for more than five years, and the first report on pediatric anesthesia was published in 2024. However, the dosage regimen for children was still unclear. The objective of our trial was to determine the 90% effective dose (ED_{90}) of remimazolam for pediatric anesthesia induction.

Methods

Our trial enrolled 45 pediatric patients undergoing ophthalmic procedures from June 2024 to September 2024. The initial induction dose was 0.2mg/kg and the sedation depth was assessed by means of the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale. The basic rule of our dose-response trial was that the dose for each patient depended on the response of the previous patient, the dose increased by 0.05mg/kg if the previous patient got a MOAA/S score greater than 1, otherwise the current dose was maintained or reduced by 0.05mg/kg at a rate of 9:1 randomly. The anesthesiologist, who assessed sedation in three minutes, was blind to the dose allocation. Subsequently, the ED_{90} of remimazolam for pediatric anesthesia induction was calculated. Additionally, the basic vital signs and adverse events during the induction were recorded.

Results

45 participants were enrolled, among which 2 were excluded due to parental refusal to participate and 43 completed the trial, 35 participants achieved positive outcomes, while 8 participants had negative outcomes. The ED_{90} of intravenous remimazolam for anesthesia induction was 0.29mg/kg (95% CI, 0.26-0.31mg/kg). The mean induction time was 125.37 ± 33.34 seconds (mean ± SD).

Conclusion

The ED_{90} of intravenous remimazolam for anesthesia induction in children was 0.29mg/kg (95% CI, 0.26-0.31mg/kg). The dose is safe and efficient for anesthesia induction in pediatric participants.

Trial registration:

The study was registered in Chinese Clinical Trial at chictr.org.cn, and the principal investigator was Hongyuan Ren.

Registration date: May 24th 2024,

First participant enrolled date: June 1th 2024,

Number: ChiCTR2400084790

URL:https://www.chictr.org.cn/showproj.html?proj=228251&u_atoken=8044a6d97e7d2997c5f6ab4b33f5cf20&u_asig=1a0c380817295931459096250e00e5

Background

The safety and efficiency of remimazolam have been proven in adult anesthesia both induction and maintance[1, 2]. In this year, several studies have shown that the remimazolam can be used in pediatric patients in general anesthesia[3] and sedation[4]. As a new brilliant sedative, its advantages has been accepted worldwide, such as rapid onset and elimination[5], no cumulative action[6], hemodynamic stability[7],and a specific antagonist[8]. It provides us a painless injection and a lower rate of postoperative nausea and vomiting (PONV) compared to propofol [9]. Furthermore, remimazolam performed a short context-sensitive half-time, a high clearance and similar pharmacokinetic properties with adults under a normalized weight[10], suggesting that it could be another excellent choice for pediatric anesthesia. Compared with adults, pediatric patients exhibit significant physiological differences, such as lower oxygen reserve, poor tolerance of hypoxia, a much larger sedative apparent volume of drug distribution which need more sedatives for getting a proper anesthesia depth[11], especially during anesthesia induction. Therefore to determine the ED_{90} for anesthesia induction was at a high priority and an optimal dosage regimen for pediatric anesthesia could offer to anesthesiologists as well.

Methods

Ethics

This study was approved by Tianjin Medical University Eye Hospital Institutional Review Board (IRB), Number :2023KY-42.

All participants' parents signed informed consent before inclusion.

Study design

Our dose-respond trial carried out a biased coin design up-and-down design(BCUD) sequential method, and the flowchart was in accordance with the CONSORT reporting guidelines[12]. Data from 45 pediatric patients who underwent strabismus, blepharoptosis, or entropion surgeries at the Tianjin Medical University Eye Hospital, Tianjin, China, from June 1st to September 30th, 2024 were included in this analysis. Our trial was carried out in accordance with the principles of the Declaration of Helsinki.

Participants

The participants who were enrolled with the age 2–12 years, 86–173 cm height, body mass index of 12–28 kg/m^2, and ASA physical status 1–2. Study staff screened, approached, and recruited participants before evaluating enrollment eligibility, obtaining informed consent, and enrolling the participants. We excluded the participants with a sore throat, an upper respiratory tract infection, potential difficult airway, high risk of pulmonary aspiration, or pharyngeal pathology.

Study method

Based on the previous reports and our experience, the initial dose was set at 0.2 mg/kg. The dose of the subsequent patient was according to the responses of the previous one by using the BCUD method. We defined the positive was sedation success: in three minutes, otherwise was negative. The dose increased by 0.05 mg/kg in the subsequent participant for negative, and the dose maintained or decreased randomly by 0.05 mg/kg at a 9:1 ratio for the positive conversely.

Sedation was assessed by using the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale, with the following criteria (Table 1): sedation success was defined as an MOAA/S score ≤ 1 at 3 minutes after a bolus dose administration, and sedation failure as an MOAA/S score > 1 at 3 minutes after a bolus dose administration.

Table 1 Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score

Score	clinical signs
5	completely awake and responded readily to their name spoken;
4	lethargic response to their name spoken;
3	patient responded after their name was called loudly and/or repeatedly;
2	patient only responded to mild pushing or shaking;
1	patient only responded to pain stimulation (trapezius squeeze)
0	patient did not respond to pain stimulation (trapezius squeeze)..

Randomization and Blinding

Identical syringes with different dose of remimazolam were prepared by a nurse. Each syringe was labeled with a unique number (0–9), and a confidential "number-dose correspondence table" (only accessible to this nurse) was used to ensure blinding. According to BCUD method, an assistant prepared the specified syring for each participant by using a computer-generated random number list before the participant and anesthesiologist arrived in the operating room. The anesthesiologist, who was blinded to the dose scheme, accessed the sedated situation of patients by using the MOAA/S score. The patients and their parents also blinded to the dosage regimen throughout the trial. There were no other anesthetics provided during this period.

Statistical Analysis

More than five crossover pairs were needed for statistical analysis of the Dixon's sequential method [13], as a result we ended the enrollment at the eighth observation of failure–success crossover pairs. We calculated the ED_{90} of remimazolam by using isotonic regression, and the bootstrapping method was applied for the 95% confidence interval (CI)[13]. We used the Pooled Adjacent Violators Algorithm (PAVA) [14] to estimate the adjusting success rate. The statistical software used was R studio for Windows version 4.4.1 and SPSS for Windows version 24.0 (SPSS Inc., Chicago, Illinois).

Sample size

Previous studies suggested that enrolling at least 20–40 participants will provide a stable estimation of the target dose for the most realistic scenarios[14]. We stopped the enrollment when 43 patients had completed the study.

Anesthesia protocol

Anesthesia protocol
The anesthesiologist did the routine pre-anesthesia visit and collected the demographic data of the patients before the procedure day. The informed consents were provided to the parents after being advised the study purpose, come with the risks and benefits.

The fasting scheme was in accordance with an international multidisciplinary consensus about fasting before procedure[15]. No premedication was provided. Intravenous access was secured to all patients who were accompanied by a parent in the anesthesia preparation room. Standard monitoring including the noninvasive blood pressure (NIBP), electrocardiography (ECG), peripheral oxygen saturation(SPO_2) and bispectral index(BIS) were conducted after the patients entered the operating theater and recorded during the induction.

Adverse events

Ephedrine (0.1mg/kg) was administered by more than 20% drop from the baseline of the NIBP, and atropine (0.01 mg/kg) was administered at the situation of the HR < 45–55 per min. The number of inotropes/vasopressors given during the induction was recorded

Results

In total, from June 1st to September 27th, 2024, 45 patients were enrolled to our trial, 2 were excluded for the parents refused to participate and a total of 43 patients successfully completed the study (Fig. 1, Flowchart). The demographic information of the patients is shown in Table 2.

Table 2 demographic data of the patients

Variables	N=43	
Age(years), mean ± SD	7.07 ± 2.59	
Height(cm), mean ± SD	129.21 ± 16.39	
Weight(kg), mean ± SD	29.30 ± 14.15	
BMI (kg/m^2), mean ± SD	16.60 ± 4.21	
Year 1-6(N=20)	13.20 ± 1.32	< BMI 95 percentile*
Year 7-12(N=21)	17.71 ± 4.41	< BMI 95 percentile**
Sex, n(%)		
Male	23(53.5)	
Female	20(46.5)	

BMI, Body Mass Index, SD, Standard deviation *< 18.1 kg/m² ≤**22.1 kg/m²

Primary outcome

The ED_{90} of intravenous injection remimazolam for anesthesia induction was 0.29mg/kg (95%CI, 0.26-0.31mg/kg). Figure 2 showed the positive and negative results of the 43 consecutive patients. The dose ranged from 0.2mg/kg to 0.35mg/kg. Table 3 showed the observed and PAVA adjusted rate for each dose level.

Table 3 the observed and PAVA adjusted rate

Assigned dose(mg/kg)	Number of patient(N)	Number of successes(N)	Observed success rate(%)	PAVA adjusted success rate (%)
0.20	1	0	0.0	0.0
0.25	10	5	50.0	50.0
0.30	22	20	90.9	74.1
0.35	12	12	100.0	100.0

Secondary outcomes

The basic life signs were stable and the BIS dropped gradually during the induction. (see Fig. 3 and Fig. 4)

No adverse events were observed during induction.

NIBP, noninvasive blood pressure, SBP, systolic blood pressure, DBP, diastolic blood pressure, MAP, mean arterial pressure

HR, heart rate, BIS, bispectral index score, RR, respiratory rate

Discussion

The main objective of our trial was to determine the ED_{90} of intravenous administration of remimazolam to achieve proper sedation during the general anesthesia induction in pediatric patients.

In our trial, we found that the ED_{90} of intravenous remimazolam was 0.29mg/kg, the 95% confidence index was 0.26mg/kg to 0.31mg/kg, and the average success time was 125.37 ± 34.33 seconds. The initial dose was determined based on our experiences and previous studies[16, 17, 18]. The BCUD method has some advantages, such as determining the ED_{90} of a certain medicine, first, an ideal target effect dose with a great clinical significance can be identify by researchers, such as 90%[19], which, second, the random method would lead a suboptimal dose to some patients rather than a high dose, which may result in a deeper sedation and even more adverse events. And a loading dose of remimazolam for adult induction was also calculated in this way[20].

Anesthesia and sedation practice in pediatrics has always been considered as a complex issue to various-field anesthesiologists, which mainly due to a more dramatic stress response to procedures in the pediatric population than in adults[21]. Moreover, invasive procedure and surgery may bring a stressful and traumatic experience to pediatric participants[22], and cause a long-term psychological problems[23, 24]. Hence, the comfortable medical services (optimized perioperative medication, decreased adverse events, and early recovery) in pediatric anesthesia had become a goal in the past decades. In our study, we found that the HR, NIBP, and RR were stable during the induction and the BIS showed a stable decrease in sedation depth, which presented a smooth and steady induction.

Remimazolam, a novel ultrashort-acting benzodiazepine[25], presents its clinical features of highly affinity with GABA receptors and revealed some characteristics from its parent compounds, midazolam and remifentanil[26]. With the outstanding pharmacological features such as high clearance rate, low distribution volumes, short half-times, rapid onset and recovery[27, 28], remimazolam presents in anesthesia with low hemodynamic fluctuations, minimal respiratory depression, and the rapid reversal by using flumazenil[29, 30]. All the features of remimazolam, especially no injection pain, made it have the capable to be a perfect choice for pediatric anesthesia induction[3, 9]. However, remimazolam also caused some adverse events, such as respiratory depress after high-dose injection[31], cannot get a proper sedation which need a rescue titration or re-sedation[32, 33] and anaphylaxis[34, 35]. Hence, our study provided an accuracy dosage regimen, which may lead a safe and efficient anesthesia induction in pediatric patients.

There were several limitations to the study. First, participants in our study with ASA physical status 1–2, lack of estimation about the participant with a more than 2 status. But our outcome would be useful to develop further discussion on whether these results can be generalized to a broader pediatric population. Second, the sample size was based on previous studies and without certain kind of calculation, so it may be insufficient in some cases. Third, such as the any previous experiences of sedation or anesthesia, real fasting time, and the sleep quality of the night before might have influence on the outcomes. Forth, the patient in our trial were aged 2–12 years, the other age intervals of children were not generalized in our trial. Last, we did not calculate the 95% effective dose, which may be more clinically relevant, and sample size were insufficient, it might be better to consider this study as a pilot study

Conclusions

The 90% effective dose of remimazolam for anesthesia induction in pediatric patients was 0.29mg/kg (95% CI, 0.26-0.31mg/kg). The dose is safe and efficient for anesthesia induction in pediatric participants.

Abbreviations

ASA
Anesthesiology Society of American
ED
effective dose
MOAA/S
Modified Observer's Assessment of Alertness and Sedation
CI
confidence interval
PONV
postoperative nausea and vomiting
BCUD
biased coin design up-and-down
PAVA
Pooled Adjacent Violators Algorithm
NIBP
noninvasive blood pressure
ECG
electrocardiography
SPO_2
peripheral oxygen saturation
BIS
bispectral index
SBP
systolic blood pressure
DBP
diastolic blood pressure
MAP
mean arterial pressure
HR
heart rate
RR
respiratory rate

Declarations

Ethics approval and consent to participate

This research followed the tenets of the Declaration of Helsinki, written informed consent was obtained from all the subjects after explanation of the nature and possible consequences of the study. This study was approved by the ethics committee of Tianjin Medical University Eye Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Author Contribution

Hongyuan Ren: Conceptualization, Methodology, Writing- Original draft preparation.Ruru Guo: Visualization, Investigation, Wei Liu: Software, Validation.Fei Gao: Software, Data curation,Yuechun Lu: Supervision, Writing-Reviewing and Editing,

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Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

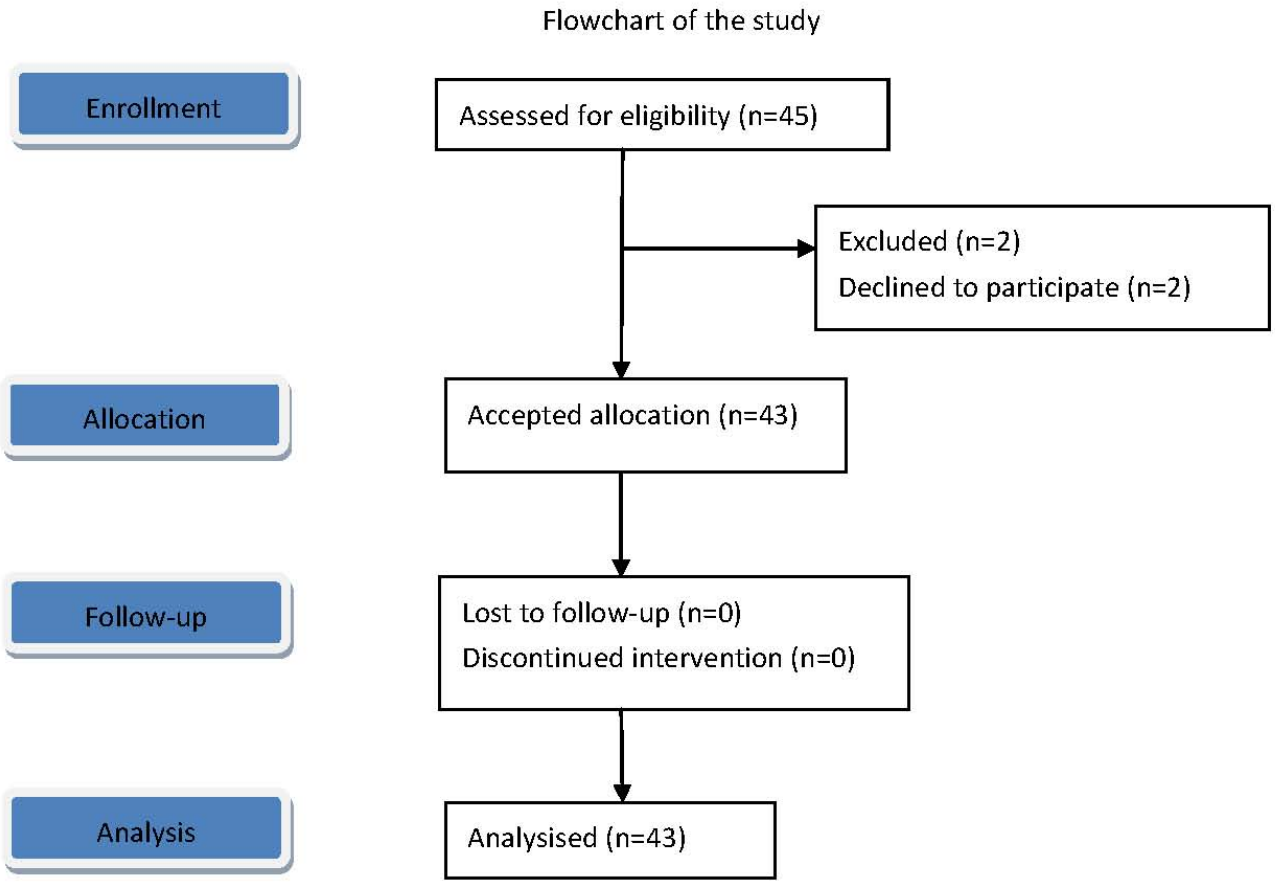


Figure 1

Flowchart of the study

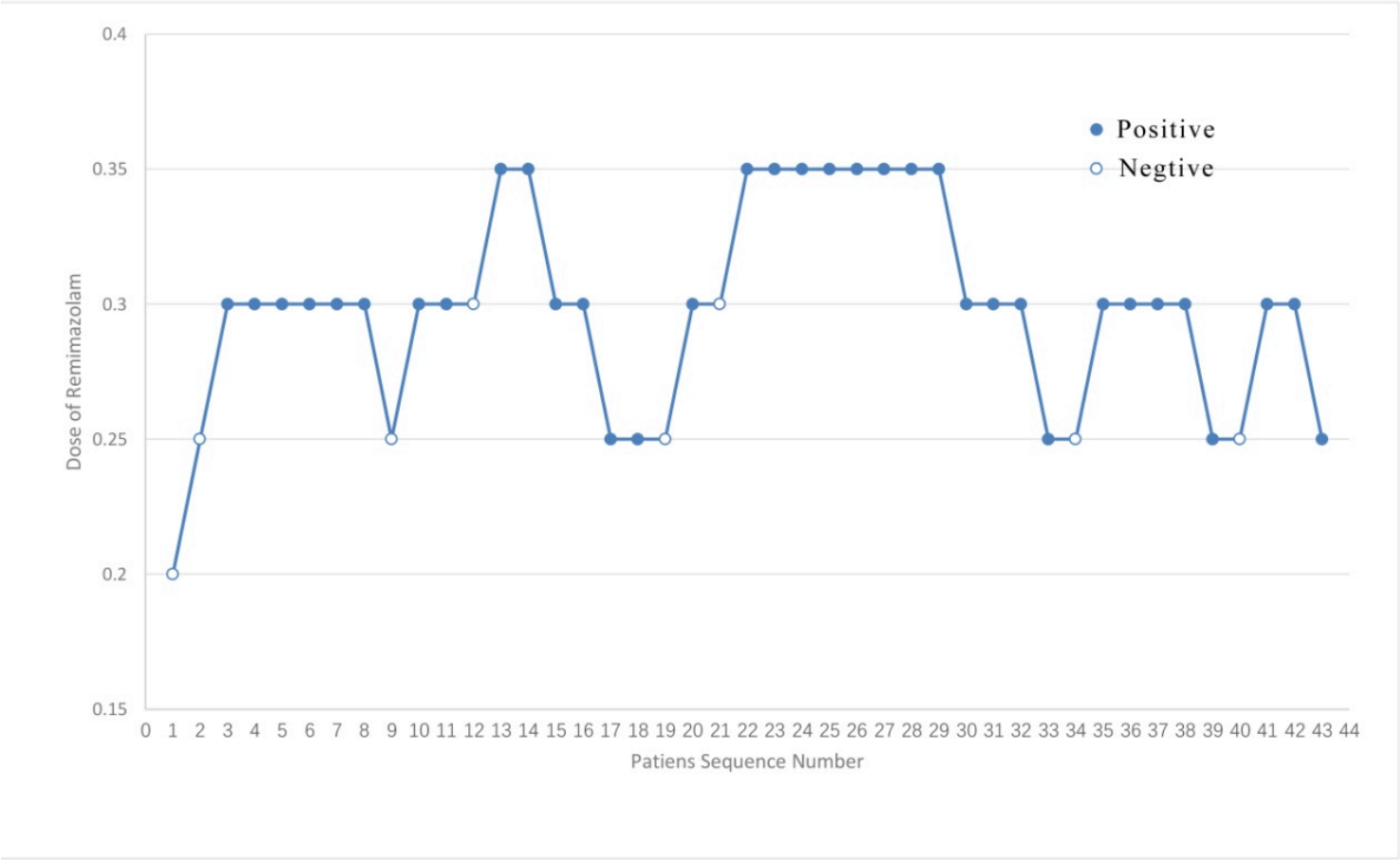


Figure 2

Results of the 43 consecutive patients

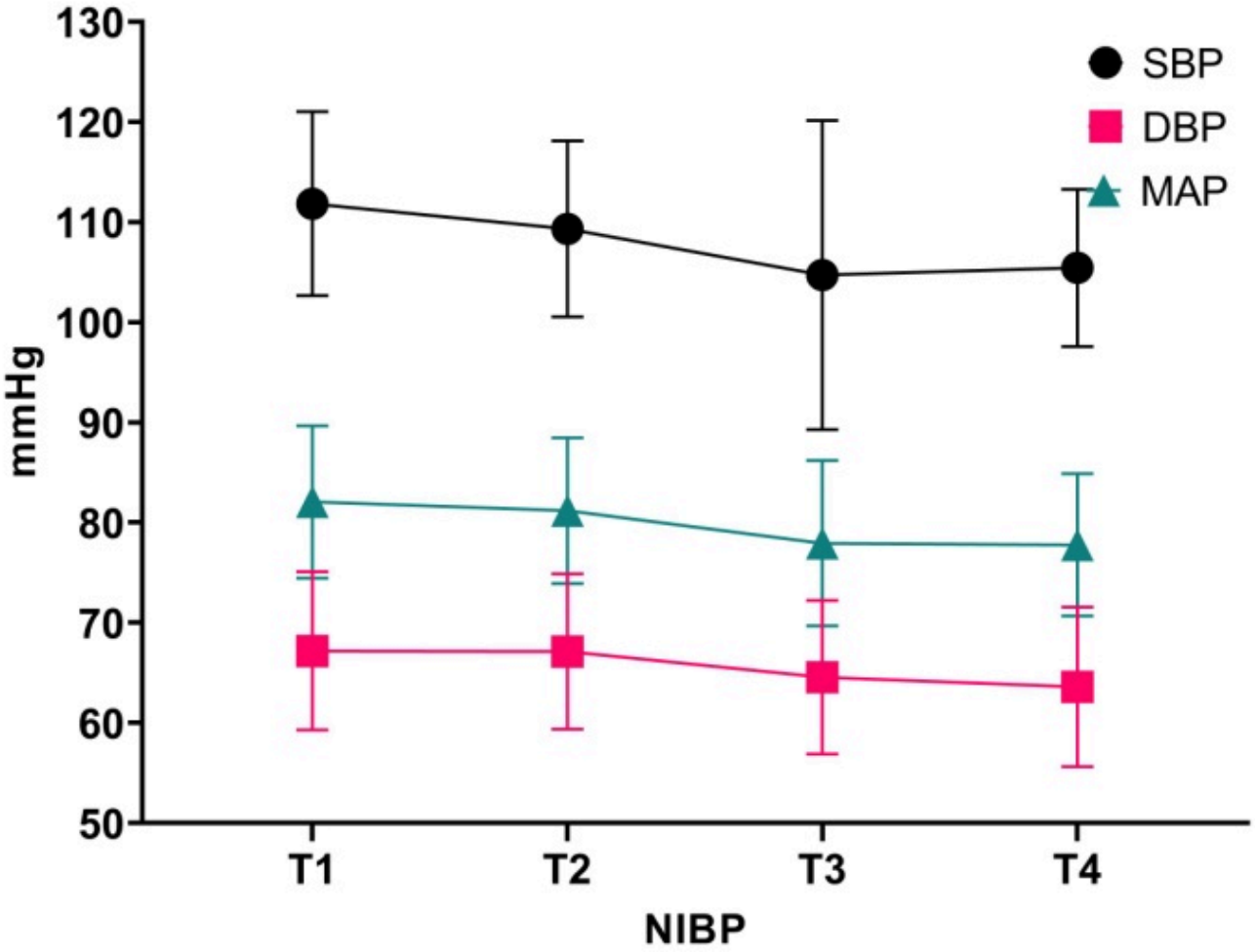


Figure 3

the variation of NIBP

NIBP, noninvasive blood pressure, SBP, systolic blood pressure, DBP, diastolic blood pressure, MAP, mean arterial pressure

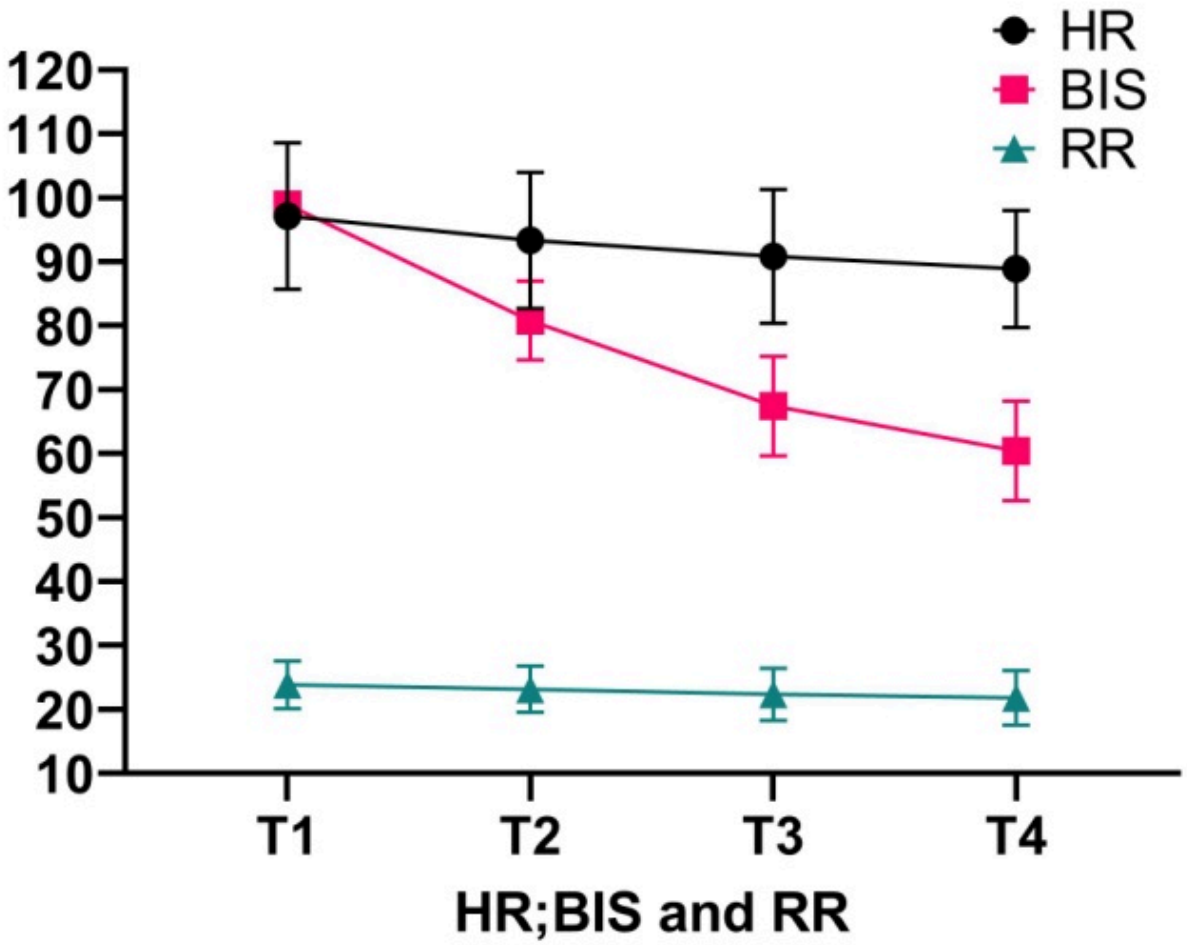


Figure 4

the variation of HR, BIS and RR

HR, heart rate, BIS, bispectral index score, RR, respiratory rate