Efficacy and Safety of Remimazolam Besylate Versus Propofol during Hysteroscopy: Single-centre Randomized Controlled Trial

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Research Article

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Abstract

Background: Remimazolam besylate is a new type of benzodiazepine that has the characteristics of quick effects, short maintenance and recovery times, and no accumulation. Compound opioids can have a sedative effect in some endoscopic examinations. This trial was conducted to confirm the efficacy and safety of remimazolam besylate versus propofol during hysteroscopy.

Methods: Patients undergoing hysteroscopy were randomly assigned to either the remimazolam (Group R, n=41) or the propofol group (Group P, n=41). Group R was administered an induction dosage of 0.2 mg/kg/min and a maintenance dosage of 1 mg/kg/h. Group P was started at 1.5-2.0 mg/kg propofol for up to 60-100 s and then maintained at 3.0-6.0 mg/kg/h. In both groups, remifentanil was infused using a target-controlled infusion system with a target concentration of 1.5 ng/ml and titrated during the procedure. The incidence rates of body movement and various adverse events in both groups were compared.

Results: Eighty-two patients were included in this study. The incidence of adverse events in Group R (8.5%) was significantly lower than that in Group P (36.6%) ($P < 0.05$). Injection pain, postoperative dizziness and low SpO_2 were the most common adverse events ($P < 0.05$). Compared with Group P patients, Group R patients recovered faster, had a shorter residence time in the PACU, and exhibited a higher quality of recovery ($P < 0.05$).

Conclusion: Remimazolam besylate can provide safe and effective sedation for hysteroscopy. The depth of sedation is sufficient and effective, and the quality of recovery is high. Moreover, adverse events such as haemodynamic fluctuation, excessive sedation depth, low SpO_2 and injection pain caused by propofol are largely avoided.

Trial registration

This study was approved by the Clinical Research Ethics Committee of Mengcheng County No.1 People's Hospital (2020MYL20003) and registered at http:// www.chictr.org.cn (15/09/2020, ChiCTR-2000038252). The study protocol is performed in the relevant guidelines.

Background

Hysteroscopy is simple and is one of the most common outpatient operations in the diagnosis and treatment of endometrial and other intrauterine diseases. The procedure has many advantages, but the main disadvantage is the strong pain due to cervical dilatation. Therefore, we believe that pain and anxiety must be decreased while providing effective sedation and analgesia during surgery to maximize patient comfort and cooperation [1–3]. To improve the comfort of patients, widely used anaesthetic methods in hysteroscopic surgery include propofol combined with opioids, propofol combined with dexmedetomidine, paracervical block, topical anaesthesia and so on [4–6].

However, in China, propofol combined with opioids is still the most commonly used method to control pain during hysteroscopy [7]. However, propofol has a high incidence of adverse events, such as injection pain, postoperative dizziness, and low SpO_2.

Remimazolam (CNS7056) is a new type of benzodiazepine that has the characteristics of quick effect, short maintenance and recovery times, no accumulation, metabolism independent of liver and kidney function, and no serious side effects. Compound opioids can have a sedative effect in some endoscopic examinations [8–10].

This trial was conducted to confirm the efficacy and safety of remimazolam besylate versus propofol during hysteroscopy.

Methods

Ethics and registration

This study was approved by the Clinical Research Ethics Committee of Mengcheng County No.1 People's Hospital (2020MYL20003) and registered at http://www.chictr.org.cn (15/09/2020, ChiCTR-2000038252). The study protocol is performed in the relevant guidelines. Written informed consent was obtained from 82 patients undergoing elective hysteroscopy of Mengcheng County No.1 People's Hospital from 15/09/2020 to 20/12/2020.

Patient inclusion and exclusion criteria

The inclusion criteria were age between 18 and 65 years old, American Society of Anesthesiologists (ASA) physical status I or II and body mass index (BMI) of 19 to 30 kg/m^2. The exclusion criteria included a history of alcoholism or allergy to general anaesthetic drugs, renal or liver diseases, communication difficulties, lactation, or recent respiratory infections.

Randomization

Patients were randomly assigned into the remimazolam group (Group R, n = 41) and the propofol group (Group P, n = 41) by a computer-generated randomization web-based, random number generator (available at http://www.random.org).

Anaesthesia

All patients fasted routinely before surgery and received no premedication. On arrival in the operating room, the Bene View N15 monitor (Mindray Biomedical Electronics Co., Shenzhen, China) was connected to monitor ECG, noninvasive blood pressure (NIBP), pulse oximetry (SpO_2), and heart rate (HR). All patients inhaled oxygen (2 L/min) through an oxygen mask, and all patients received intravenous flurbiprofen axetil 50 mg (Wuhan Docan Pharmaceutical Co., Ltd., China) for analgesic preconditioning before the start of hysteroscopy.

Grouping and intervention

All patients in Group R were started at an induction dosage of 0.2 mg/kg/min remimazolam besylate (Yichang Humanwell Pharmaceutical Co., Ltd. China) and a maintenance dosage of 1 mg/kg/h by continuous intravenous (IV) infusion until the loss of consciousness (LoC) [11, 12]. When the eyelash reflex disappeared and the MOAA/S score was ≤ 2 (Table 1) [13, 14], hysteroscopy was started. According to the MOAA/S score, remimazolam was added at 2.5 mg/dose, with no more than 5 doses administered within 15 min [15].

Table 1
Description of the Modified Observer's Alertness/Sedation (MOAA/S) scale.

Scores	Score Description
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

All patients in Group P were started at 1.5-2.0 mg/kg propofol (Fresenius Kabi AG Austria) for up to 60–100 s. When the eyelash reflex disappeared and the MOAA/S score was ≤ 2, hysteroscopy was started. Then, the cells were maintained with 3.0 mg/kg/h propofol at the same time. According to the MOAA/S score, the injection speed of propofol was adjusted to 3–6 mg/kg/h [16].

The induction of remifentanil (Yichang Humanwell Pharmaceutical Co., Ltd. China) in the two groups was performed by a target-controlled infusion (TCI) pump (Guangxi VERYARK Technology Co., Ltd, China), and the effective effect-site concentration (Ce) (Minto pharmacokinetic model) was 1.5 ng/ml [16, 17]. Remifentanil was increased by 0.5 ng/ml when insufficient analgesic effects, such as distorted facial expressions; musculoskeletal, connective tissue and connective tissue disorders; blood pressure (SBP) > 140 mmHg; or tachycardia (heart rate [HR] > 100 beats/min (bpm) or sudden increase of more than 30 bpm over baseline.

Outcomes

Primary outcome

The primary outcome of this study was the incidence of body movement and various adverse events, such as injection pain ('subjective' assessment, namely, patients verbally reported their pain by

themselves after the first injection), postoperative dizziness (while patients stayed in the PACU), low SpO_2 ($SpO_2 \leq 95\%$ during anaesthesia), bradycardia (HR < 55 bpm during anaesthesia) and hypotension (SBP 90 mmHg during anaesthesia). The treatment for these events was the titration of ephedrine, atropine, and, if necessary, mandibular ventilation.

Secondary outcome

Patient data included the MAP, HR, SpO_2, and MOAA/S score at preanaesthesia (T0), postanaesthesia (2 min, T1), cervical dilatation (T2), end of the operation (T3), and awakening (T4).

Sample size and statistical analysis

In the pilot study on the combined use of propofol and remifentanil in hysteroscopy, the incidence of various intraoperative adverse events was 30%. This result indicated a clinically significant reduction in the incidence of adverse events to 5% by the use of remimazolam. The sample size of 41 participants in each group was calculated, and the significance level was 0.05 (a = 0.05). Given the 10% abortion rate, the strength was 80% (b = 0.20) [18].

Statistical analysis was performed using SPSS Statistics 17.0.1 (SPSS Inc., Chicago, IL). Data are expressed as the means ± standard deviations for continuous variables (e.g., demographic data, haemodynamic variables) or as the number (percentage) of patients (e.g., for intraoperative pain and the incidence of various adverse events). A P value < 0.05 was considered to indicate statistical significance.

Results

The study population comprised 82 randomly coded patients in Group R (n = 41) and Group P (n = 41) (Fig. 1).

Demographic data and surgical characteristics

The demographic characteristics of the patients and surgical characteristics are given in Table 2. The age, height, weight, BMI and ASA between the two groups were not significantly different (all P > 0.05). Hysteroscopic surgery was successful in the two groups. The durations of the operation in the two groups were similar (P > 0.05). The awakening time of Group R (199.0 ± 79.9 s) was significantly greater than that of Group P (59.7 ± 1.2 s) (P < 0.05). However, the PACU length of stay in Group R (5.44 ± 1.0 min) was significantly shorter than that in Group P (6.3 ± 1.9 min) (P < 0.05). The total remifentanil dosing among the two groups was not significantly different (P > 0.05).

Table 2
Demographic characteristics and clinical data for each group.

	Group R (n = 41)	Group P (n = 41)	P value
Age (year)*	43.8 ± 8.0	45.2 ± 7.0	0.39
Height (cm) *	159.6 ± 5.2	160.0 ± 4.9	0.74
Weight (kg)*	62.8 ± 7.6	61.6 ± 8.2	0.49
BMI (kg/m^2)*	24.7 ± 2.7	24.1 ± 2.8	0.33
ASA (□/□) (n)	28/13	34/7	0.12
Duration of operation (min)	13.2 ± 4.2	12.6 ± 4.7	0.50
Duration of awakening (s)**	199.0 ± 79.9	59.7 ± 1.2	0.001
PACU length of stay (min)***	5.44 ± 1.0	6.3 ± 1.9	0.02
Total remimazolam (mg)	22.6 ± 4.6	—	—
Total propofol (mg)	—	150.0 ± 32.7	—
Total remifentanil (μg)	75.7 ± 15.2	73.2 ± 22.2	0.55
Note: Data are the mean ± SD or n; ASA - American Society of Anesthesiologists; BMI - body mass index; PACU - postanaesthesia care unit.			
*Demographic data and surgical characteristics were not significantly different between the 2 groups			
**Defined as the end of infusion to the eyes opening upon calling			
***Defined as the arrival of the Steward recovery score ≥ 4			

Adverse events

Adverse events occurred in 21 (8.5%) subjects in group R and 90 (36.6%) subjects in group P, with no serious adverse events or deaths occurring in the two groups ($P < 0.05$, Table 3). The incidence of injection pain in Group P (33/41, 80.5%) was much higher than that of injection pain in Group R (1/41, 2.4%) ($P < 0.05$). The incidence of other adverse events, such as postoperative dizziness, low SpO_2 ($SpO_2 \leq 95\%$), bradycardia (HR□55 bpm), and hypotension (SBP□90 mmHg), in Group P was lower than that in Group R ($P < 0.05$). During the examination, 15 and 20 patients in Group R and Group P, respectively, exhibited slight body movement, but this did not interfere with the operation or cause dropout from the research ($P > 0.05$).

Table 3
The incidence of intraoperative adverse events.

Adverse events	Group R (N = 41)	Group P (n = 41)	P value
Injection pain	1 (2.4%)	33 (80.5%)	0.001
Body movement	15 (36.6%)	20 (48.8%)	0.26
Postoperative dizziness	0 (0.0%)	10 (24.4%)	0.001
Low SpO_2 ($SpO_2 \leq 95\%$)	4 (9.8%)	21 (51.2%)	0.001
Bradycardia (HR 55 bpm)	0 (0.0%)	1 (2.4%)	0.31
Hypotension (SBP 90 mmHg)	1 (2.4%)	5 (12.2%)	0.09
Total	21 (8.5%)	90 (36.6%)	0.03
Note: Values as n (%); HR-heart rate; SBP-systolic blood pressure			

Changes in circulation

Compared with T0, the MAP, HR, and SpO_2 at T1–4 in the two groups were all reduced (all $P < 0.05$), but all values were within the clinically normal range (Figs. 2–4). During sedation, only one patient in Group P had bradycardia (HR < 60 bpm), but this condition improved rapidly. Hypotension and bradycardia in both groups were not associated with ephedrine or atropine. Compared to Group P, Group R showed less fluctuation in MAP, HR, and SpO_2.

MOAA/S score

In this study, the rate of sedation success in the two groups was 100%, and the patients in the two groups did not take any medicines or withdraw from the study due to insufficient sedation. The MOAA/S scores in the two groups during hysteroscopy indicated that the depth of sedation was adequate and effective (Fig. 5).

Discussion

Throughout this study, we observed no serious adverse events or adverse reactions in the two groups that would require withdrawal from the trial. The incidence of adverse events in Group R (21/246, 8.5%) was significantly lower than that in Group P (90/246, 36.6%) ($P < 0.05$). Injection pain, postoperative dizziness and low SpO_2 were the most common adverse events (Table 3, $P < 0.05$).

In a previous multicentre phase III clinical trial in China, the remimazolam group had a lower incidence of hypotension (46 (23.71%) versus 97 (51.05%)) and respiratory depression (6 (3.09%) versus 32 (16.84%)) than the propofol group [19]. In another study, 5.6% of the patients in the remimazolam group had serious adverse events compared with 6.8% in the placebo group [20]. Our experiment further confirmed those results.

Injection pain is one of the most common adverse reactions of propofol in clinical work. At present, the methods to relieve the injection pain of propofol include large vessel injection, slowing down of the injection speed or combined application of auxiliary drugs, such as lidocaine, opioid analgesics, and preoperative oral paracetamol [21]. Remidazolam has the same sedative effect as propofol, effectively avoiding the adverse reactions of injection pain to improve the comfort of patients.

In our study, the success rate of sedation in the two groups was 100%, and the patients in the two groups did not use remedial drugs or withdraw from the trial due to insufficient sedation depth. After the first administration of the drug, the patients in the two groups achieved enough depth of sedation within a short period of time and met the requirements of hysteroscopy at the beginning of sedation.

In Group R, the patients recovered faster, the residence time in the PACU was shorter than that of Group P, and the quality of recovery was higher ($P < 0.05$). In another multicentre phase III trial, researchers also found that remimazolam (5.75 min) yielded a faster recovery from sedation than propofol did (6.71 min). This is a potential benefit of remimazolam over propofol [22]. It can be speculated that both remimazolam and propofol can meet the required sedation depth and maintenance time for uterine cavity examination but that the sedation of remimazolam can avoid the phenomenon of deep sedation in the propofol group and has little effect on the inhibition of the central nervous system of patients.

Remimazolam has the advantages of rapid onset, a short elimination half-life, and drug metabolism that is independent of liver and kidney function [23]; moreover, it has a specific antagonist, namely, flumazenil [24]. Compared with midazolam, remimazolam provides effective procedural sedation, and the success rate and recovery rate are higher than those of midazolam. At present, there is a lack of data in comparison with propofol. As a benzodiazepine, remimazolam will be widely used in preoperative medication, endoscopy, induction and maintenance of general anaesthesia, and sedation of ICU patients in the future [25]. In previous studies, remimazolam was used effectively and safely in Chinese volunteers [21, 26].

There are some limitations in this study. This was a single-centre investigation, and the sample size was relatively small, which limited the ability of statistical analysis between the two groups of patients.

Conclusions

Remimazolam besylate can provide safe and effective sedation for hysteroscopy. The depth of sedation is sufficient and effective, and the quality of recovery is high. Moreover, adverse events such as haemodynamic fluctuation, excessive sedation depth, low SpO_2 and injection pain caused by propofol are largely avoided. However, the cases involved in this study were all from a single centre, and the relevant conclusions need further analysis and study of multiple centres and costs.

Abbreviations

ASA = American Society of Anesthesiologists, BMI = body mass index, EEG =electroencephalography, HR = heart rate, MAP = mean arterial pressure, MOAA/S = Modified Observer's Alertness/Sedation, PACU = postanaesthesia care unit, SBP= systolic blood pressure

Declarations

The authors declare that they have no competing interests

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of Mengcheng County No.1 People's Hospital (2020MYL20003) and registered at http:// www.chictr.org.cn (15/09/2020, ChiCTR-2000038252). The study protocol is performed in the relevant guidelines. Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to institutional restrictions but are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no conflicts of interest.

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This study was self-financed.

Authors' contributions

Xiaoqiang Zhang, Shuang Li and Jing Liu designed the study. Shuang Li and Jing Liu recruited patients. Shuang Li performed statistical processing and wrote the manuscript. Xiaoqiang Zhang revised the manuscript. All authors are aware of and responsible for the research data. All authors read and approved the manuscript in its final version.

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Figures

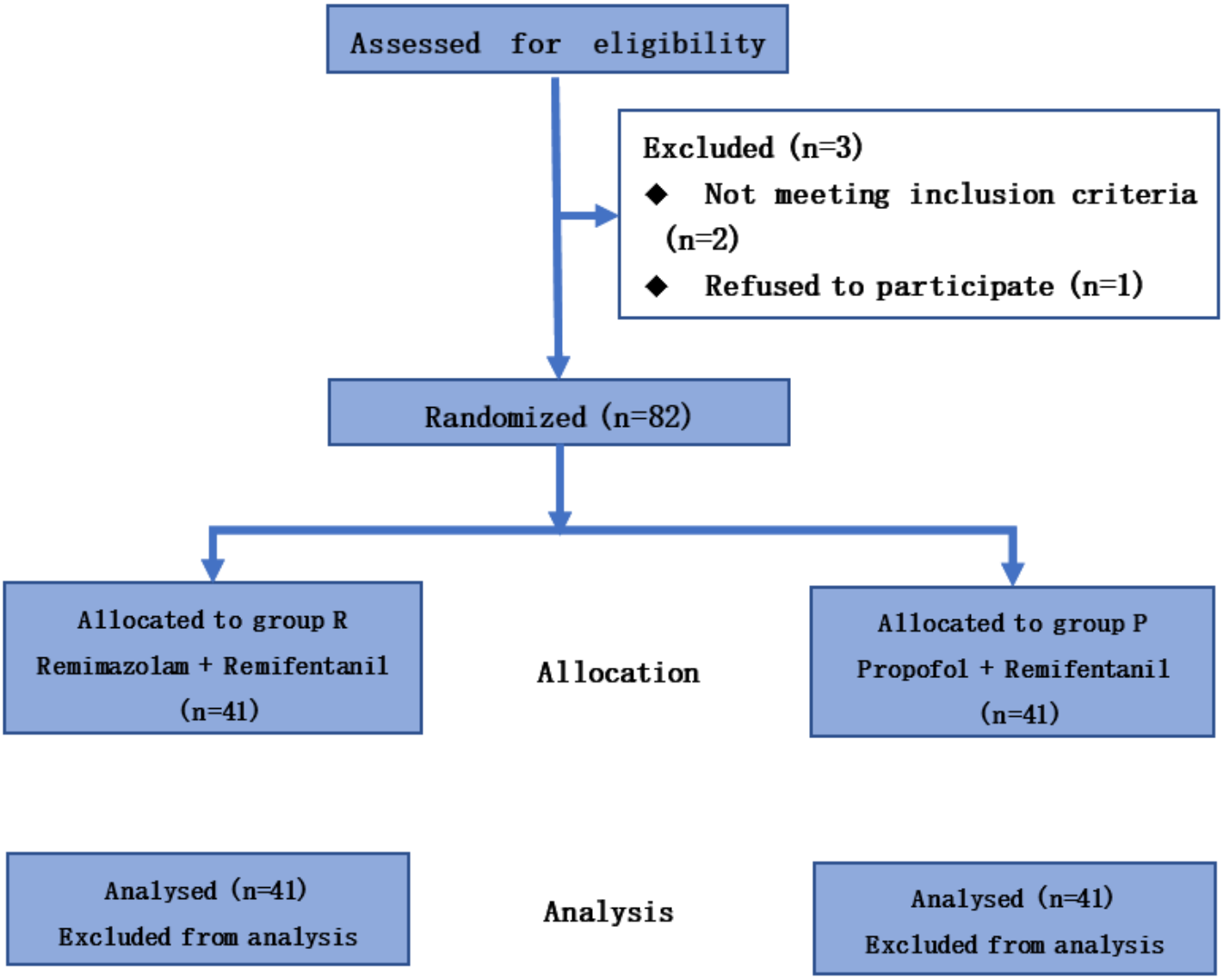

Figure 1

Flow diagram of the study

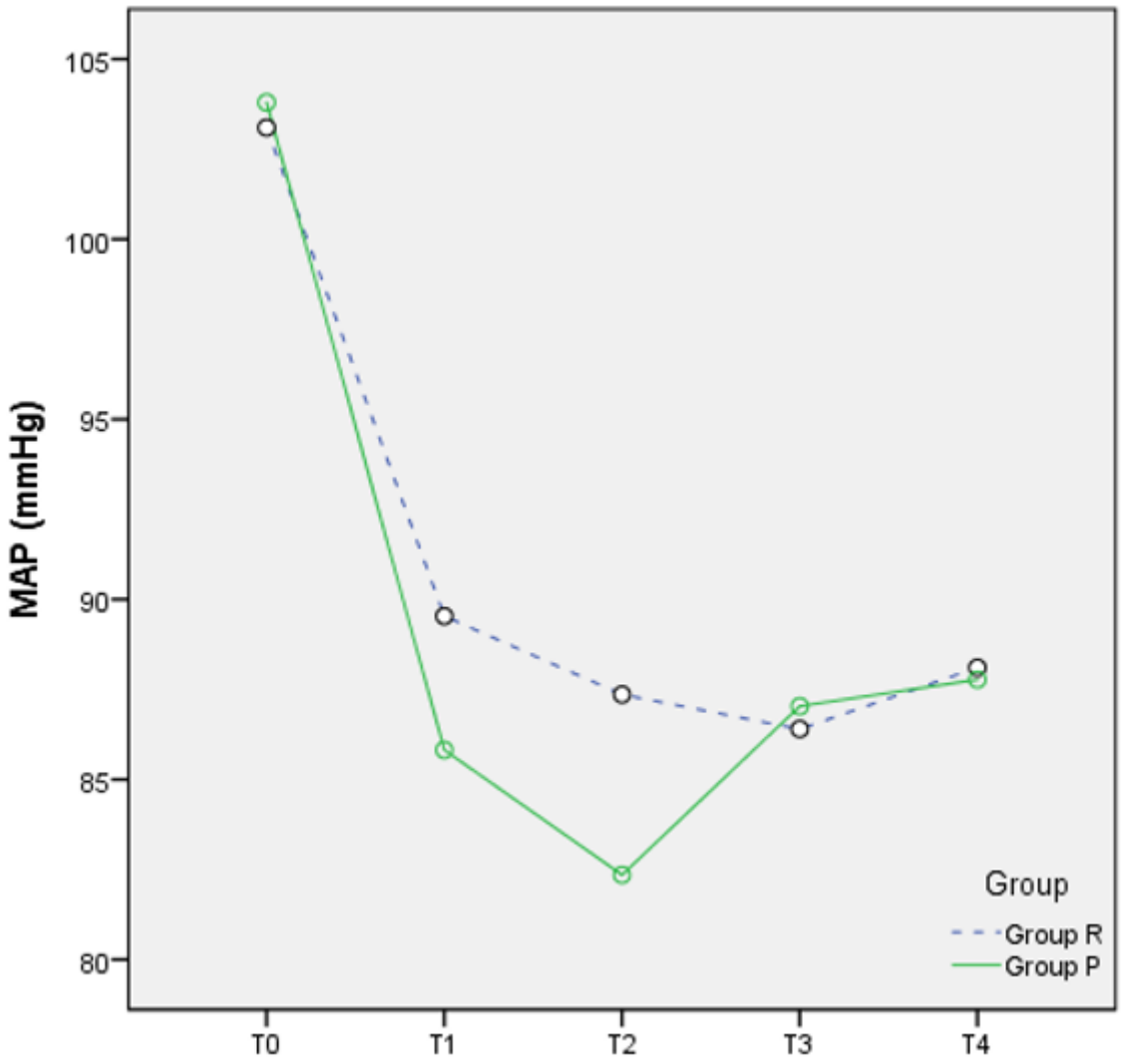

Figure 2

Mean arterial pressure (MAP)-time graphic

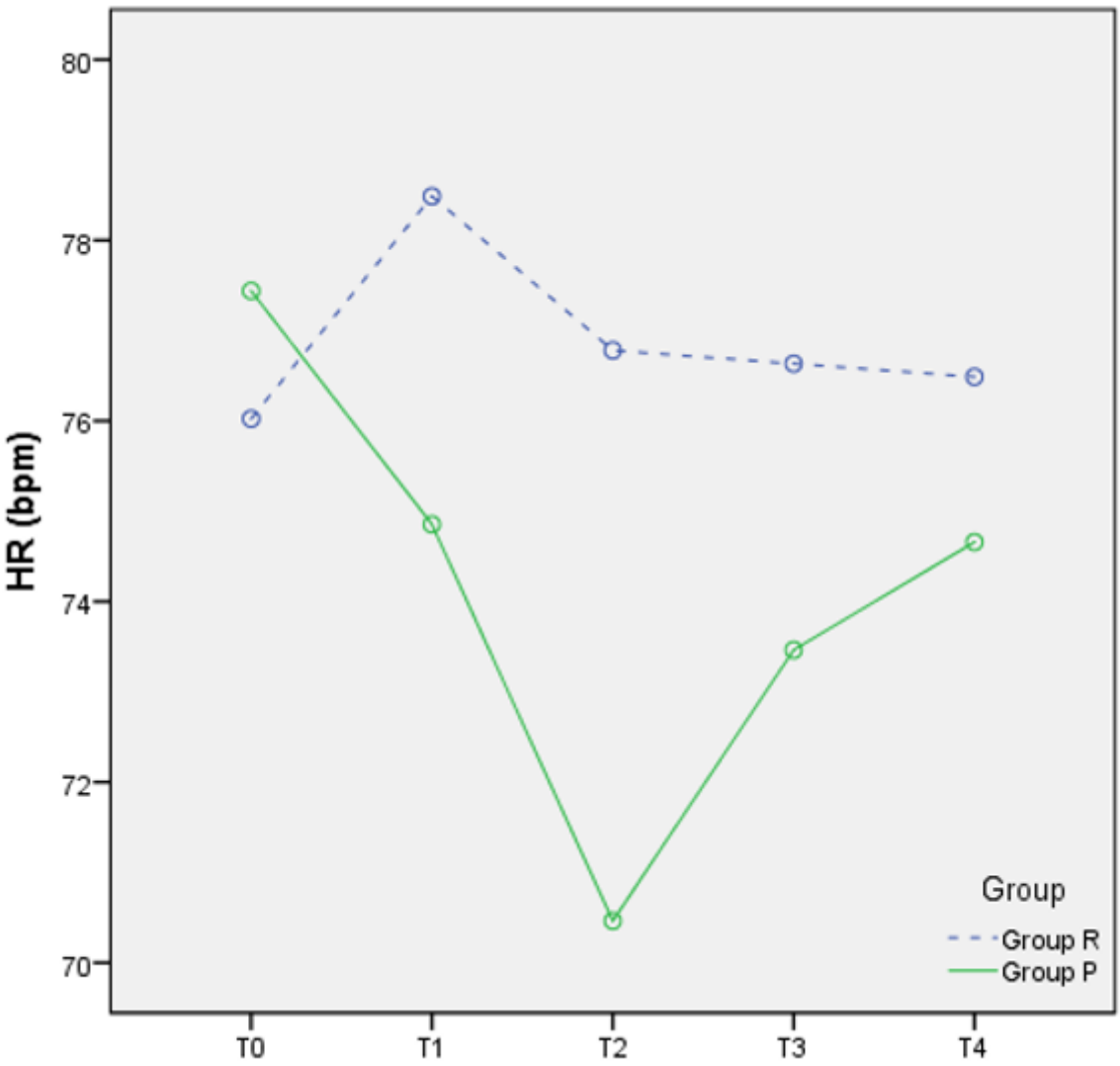

Figure 3

Heart rate (HR)-time graphic

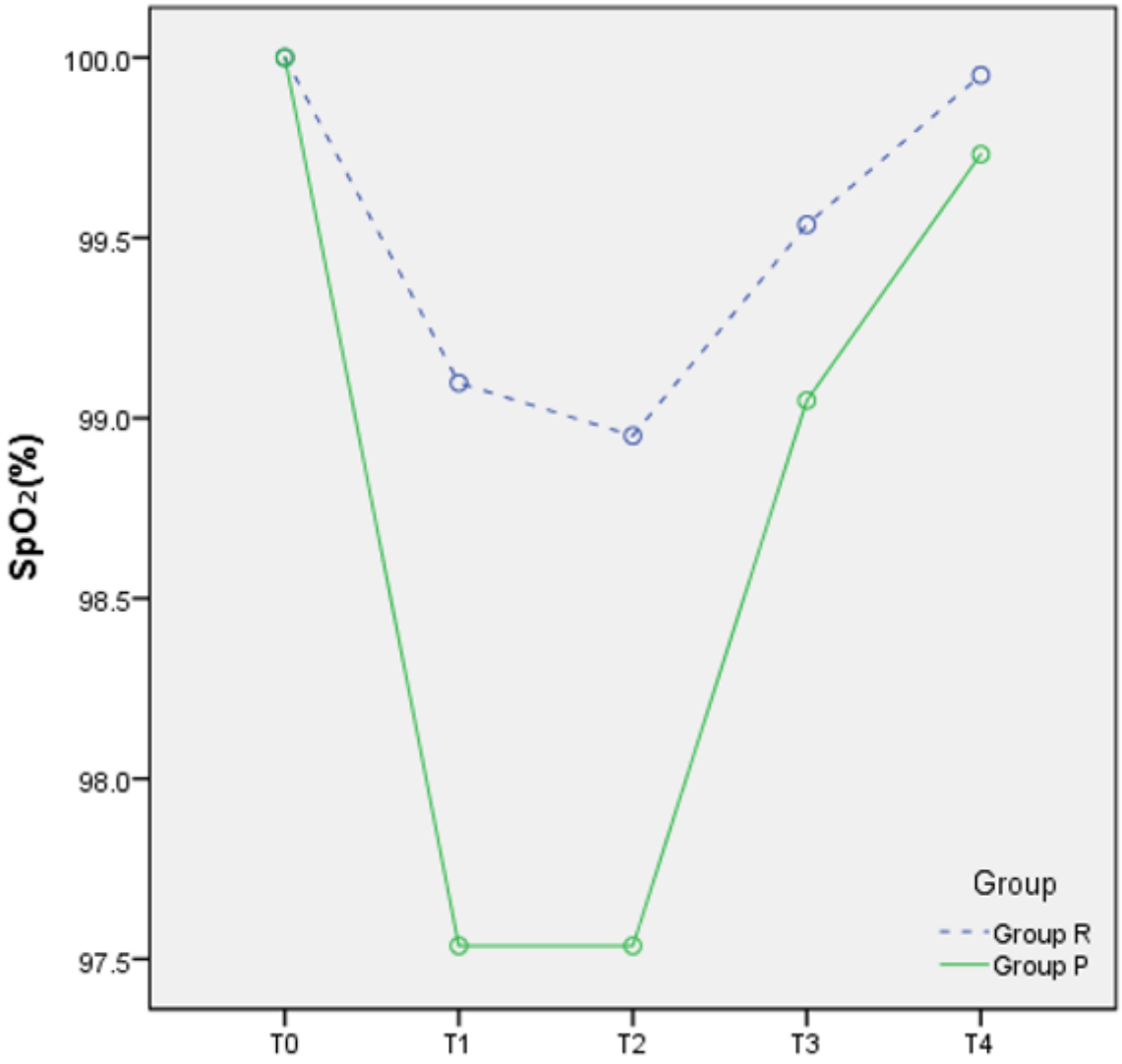

Figure 4

SpO2-time graphic

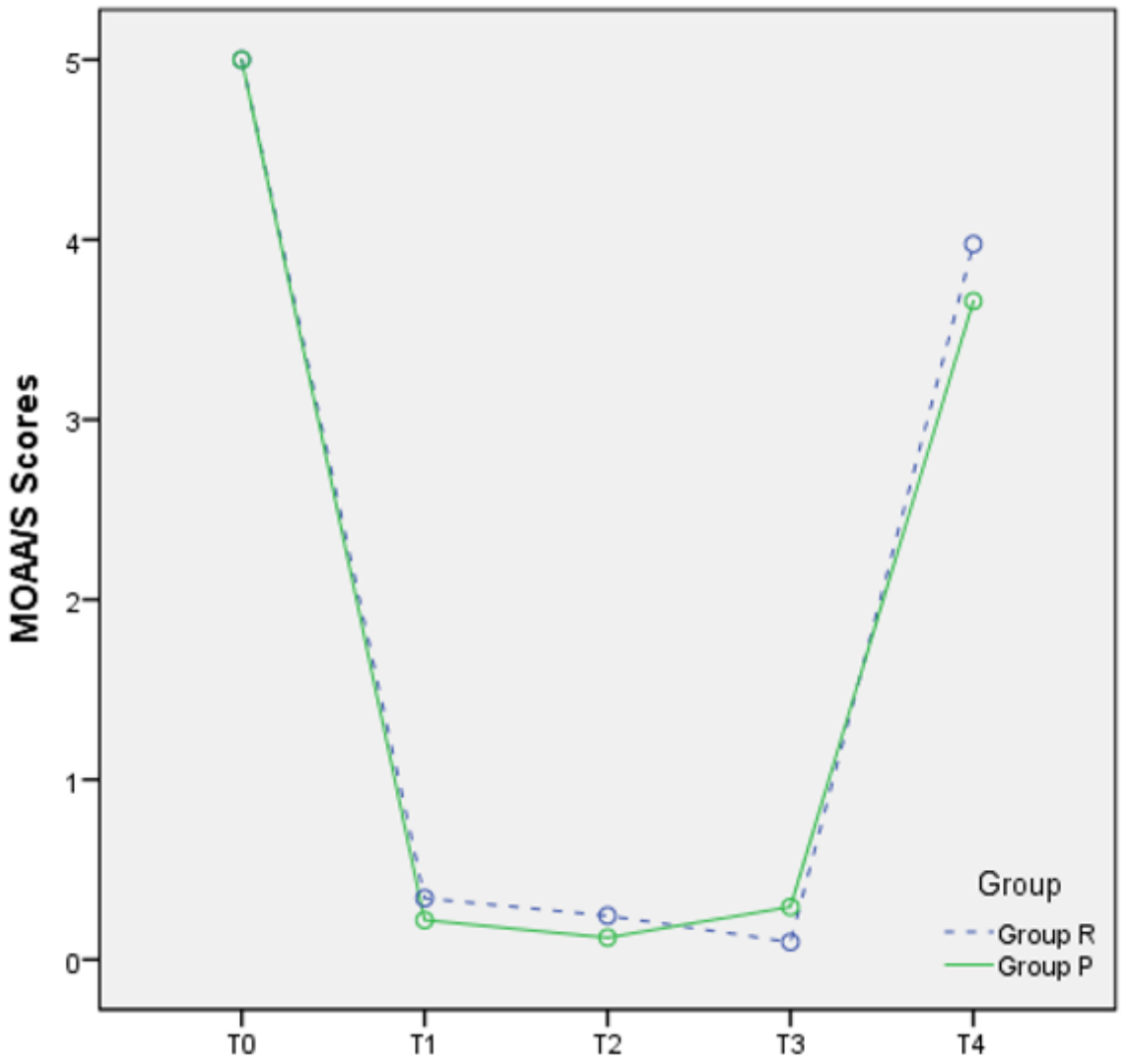

Figure 5

MOAA/S-time graphic