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Research Article

Keywords: Dexmedetomidine, Sedative and analgesic anesthesia, Loading dose, Hemodynamics, Respiration

Posted Date: December 17th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-118129/v1>

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Comparison of the efficacy and safety of dexmedetomidine administrated in two different modes in sedative and analgesic anesthesia: a randomized controlled trial

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Abstract

Background: To observe and compare the efficacy and safety of dexmedetomidine administrated in two different modes in sedative and analgesic anesthesia.

Methods: Sixty female patients, of American Society of Anesthesiologists physical status I or II, aged from 18-52 years and scheduled for elective plastic operations under sedative and analgesic anesthesia were randomly divided into a control group and an intervention group, with 30 patients in each group. All patients were administered IV midazolam 0.04mg/kg and a continuous infusion of 0.1 µg/kg/min of remifentanyl at the beginning of anesthesia. Patients in the control group received IV dexmedetomidine (DEX) 1 µg/kg over 15 min followed by 0.4-0.7 µg/kg/h infusion while patients in the intervention group received IV DEX 1 µg/kg over 30 min followed by 0.4-0.7 µg/kg/h infusion. Heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), bispectral index (BIS) and Ramsay sedation scores (RSS) were recorded. The lowest respiratory rates (LRR), incidences of respiratory depression, incidences of oxygen supplementation by facial mask and thrusting the jaw, frequencies of body movements, and additional rescue drug administrations were also recorded. After surgery, recovery time, recall of intraoperative events, pain scores in postanesthesia care unit(PACU), and

satisfaction of patients and surgeons were assessed.

Results: The BIS at time points from 5 min after anesthesia to the end of surgery in the intervention group were significantly higher than those in the control group ($P<0.05$). The RSS scores at time points from 5 min after anesthesia to immediately after induction with DEX were significantly higher in the intervention group than those in the control group ($P<0.05$). The HR at time points from the beginning of surgery to 30 min after local anesthesia, the MAP at time points from 30 min after local anesthesia to the end of surgery, and the RR at time points from 5 min after anesthesia to the end of surgery were significantly higher in the intervention group than those in the control group ($P<0.05$). Compared with the control group, patients in the intervention group had higher LRR, lower incidences of respiratory depression, more oxygen supplementation by facial mask and thrusting the jaw, and a shorter recovery time ($P<0.05$).

Conclusions: The two different dexmedetomidine administrations effectively sedated and provided analgesia for patients. Dexmedetomidine infused with a loading dose over 30 min had less impact on patients' hemodynamics and respiration and could shorten the recovery time after anesthesia.

Trial registration: Registered at the Chinese Clinical Trial Registry, registration number ChiCTR1900027958, date of registration: 07/12/2019.

Key words: Dexmedetomidine; Sedative and analgesic anesthesia; Loading dose; Hemodynamics; Respiration

Background

Dexmedetomidine (DEX) has been used extensively in various superficial surgical procedures and sedation radiographic tests as it induces sedation, analgesia and anxiolysis without significant respiratory depression [1]. DEX is currently administrated as a loading dose over 10-15 minutes to rapidly achieve a certain blood concentration, followed by a continuous infusion [2]. Due to the limited strength of its sedative and analgesic effects, DEX is often administrated to patients with other

analgesics or narcotic drugs in sedative and analgesic anesthesia. When used in combination, DEX can improve the anesthetic effect, but may also act to increase the risk of intraoperative respiratory depression [3]. Combination of DEX with remifentanyl can induce cardiovascular complications such as a lower heart rate [4]. Previous research reported that omitting the loading dose of DEX avoided haemodynamic side effects without compromising sedation and analgesia [5]. No investigation has yet to evaluate whether the prolonged loading dose time of DEX would produce comparable anesthetic effect and decrease the incidences of side effects. With an emphasis on the quality of anesthesia, we designed this study to determine whether the difference in loading dose infusion time would produce different efficacy and safety in sedative and analgesic anesthesia during plastic surgeries.

Methods

Patients

The study protocol was approved by Ethic Committee of Plastic Surgery Hospital, Chinese Academy of Medical Science (2016-12) and written informed consent was obtained from each patient prior to start. The study was conducted in compliance with the recommendations of the CONSORT Statement and the Declaration of Helsinki. The trial was registered at the Chinese Clinical Trial Register, registration number ChiCTR1900027958. A total of 60 female patients, American Society of Anesthesiologists (ASA) physical status class I or II, aged 18–52 years, and scheduled for elective plastic surgery under sedative and analgesic anesthesia were enrolled in this trial. The patients were allocated randomly to one of the two groups (n=30) using a computer-generated list of random numbers. Exclusion criteria were: bradycardia (HR < 50 beat/min), hypotension (Mean arterial pressure [MAP] < 60 mmHg), severe disease (heart, pulmonary, hepatic or renal), obesity (Body mass index [BMI] ≥ 30), obstructive sleep apnea/hypopnea syndrome, and known allergy to DEX.

Monitoring indicators

No premedication was given to any of the patients. After being taken to the operating room, standard monitoring included electrocardiogram (ECG), noninvasive blood

pressure (BP), heart rate (HR) and oxyhemoglobin saturation (SpO₂) (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland). Respiratory rate (RR) was monitored by a nasal end-tidal CO₂ cannula. The bispectral index (BIS) was also continuously monitored (BIS Vista, Covidien, Boulder, CO, USA). A peripheral intravenous (IV) catheter was inserted by nurse.

Anesthesia management

All patients received an IV of midazolam (0.04mg/kg) and a continuous infusion of remifentanyl (0.1 µg/kg/min) at the beginning of anesthesia. Patients in the control group received IV DEX 1 µg/kg over 15 min followed by 0.4-0.7 µg/kg/h infusion and patients in the intervention group received IV DEX 1 µg/kg over 30 min followed by 0.4-0.7 µg/kg/h infusion. During the surgery, the level of sedation status was assessed using the Ramsay Sedation Scores (RSS) [6] (Table 1) and the BIS. The goal of sedation was to achieve an RSS of 3-5 or BIS of 60–80. Therefore, local anesthesia was performed. The patients' MAP and HR were maintained at a range of baseline ± 20%. Atropine (0.3 mg) and ephedrine (6 mg) were intravenously administered for bradycardia (HR < 50 beats/min for > 60 s) and hypotension (MAP < 60 mmHg for > 60 s), respectively. A facial oxygen mask (6 L/min) was used for hypoxia (SpO₂ < 90%). If airway obstruction occurred, the patient was treated by thrusting the jaw. Midazolam (2 mg) was administered as a rescue drug when the infusion rate of DEX was increased to a maximum of 0.7 µg/kg/h and the depth of sedation was not achieved. The infusion of DEX was stopped 30 min before the end of surgery, and the infusion of remifentanyl was turned off at the end of the surgery.

Outcome measurements

HR, MAP, RR, BIS, RSS were evaluated and recorded before anesthesia (baseline) (T₀), 5 min after anesthesia (T₁), 10 min after anesthesia (T₂), immediately after induction with DEX (T₃), the beginning of local anesthesia (T₄), the beginning of surgery (T₅), 30 min after local anesthesia (T₆), 60 min after local anesthesia (T₇), immediately after turning off DEX infusion (T₈), and the end of surgery (T₉). The lowest respiratory rates (LRR), incidences of respiratory depression (RR < 10 breaths/min), incidences of

oxygen supplementation by facial mask and thrusting the jaw, frequencies of body movements, and additional rescue drug administrations were also recorded throughout the procedure. After surgery, recovery time, recall of intraoperative events, and pain scores using a numerical pain scale (0 = no pain to 10 = the worst pain) [7] in PACU were assessed. The satisfaction of patients and surgeons with the anesthesia were assessed using a 5-point numerical rating scale [8] (Table 1).

Table 1. Satisfaction scale and Ramsay sedation scores

Satisfaction scale	
0	Extremely dissatisfied
1	Dissatisfied
2	Neutral
3	Satisfied
4	Extremely satisfied
Ramsay sedation scores	
1	Anxious and agitated, restless
2	Cooperative, oriented, tranquil
3	Responsive to verbal commands, drowsy
4	Asleep, responsive to light stimulation
5	Asleep, slow response to stimulation
6	No response to stimulation

Statistical analysis

Calculation of sample size was based on the primary endpoint of BIS value immediately after induction with DEX (T3). In our pilot study, the BIS value (T3) in the control group was 65.9 ± 5.72 . A power analysis with a two-sided significance alpha level of 0.05 and a power of 0.8 indicated that a sample size of 21 patients in each group was enough to detect a 5 difference in BIS value after induction with DEX. We aimed to recruit 30 patients in each group to account for the possible exclusions and dropouts.

All statistical analyses were performed using SPSS 17.0 (SPSSFW, SPSS Inc.). The normality of distribution was assessed with the Shapiro-Wilk test. Normally distributed data are presented as mean \pm SD, and skewed data were presented as a median with an interquartile range [IQR]). Independent t-test was used to examine the difference of normally distributed continuous variables between groups. Skewed data were analyzed by Mann-Whitney U-test. Categorical data are presented by frequency and analyzed by χ^2 test. A *P* value of < 0.05 was considered statistically significant.

Results

The procedure was successfully performed in each of the 60 patients recruited in the study. In the end, all of the 60 patients (30 in the control group and 30 in the intervention group) were included in the final analysis (Figure 1). No significant differences were observed in patient demographic data including gender, age, ASA classification and BMI (Table 2). The surgery time did not differ between groups.

Figure 2 and Table 3 show the changes in sedation level during the study. Patients in the intervention group had higher BIS at time points from 5 min after anesthesia to the end of surgery ($P<0.05$). Patients in the intervention group also had higher RSS scores compared with the control group at time points from 5 min after anesthesia to immediately after induction with DEX ($P<0.05$).

Figure 3 displays the hemodynamic and respiratory parameters changes during the study. Patients in the intervention group had higher HR at time points from the beginning of surgery to 30 min after local anesthesia, higher MAP at time points from 30 min after local anesthesia to the end of surgery, and higher RR at time points from 5 min after anesthesia to the end of surgery ($P<0.05$).

Compared with the control group, patients in the intervention group had higher LRR, lower incidences of respiratory depression, lower incidences of oxygen supplementation by facial mask and thrusting the jaw, and a shorter recovery time ($P<0.05$) (Table 4).

No significant differences were found in body movements, additional rescue drug administrations, recall of intraoperative events, pain scores and the satisfaction levels of patients and surgeons between groups ($P>0.05$) (Table 4).

Table 2. Patients' demographic data and surgery time

	Control Group	Intervention Group	<i>P</i> value
Gender (M/F)	0/30	0/30	1.000
Age (yrs)	32.2±8.4	30.2±6.3	0.301
BMI (kg/m ²)	21.5±2.6	20.4±2.4	0.075
ASA (I/II)	30/0	30/0	1.000
Surgery time (min)	123.0±37.9	125.0±64.9	0.888

Values are mean±SD or number

Table 3. Ramsay sedation scores

	Control Group	Intervention Group	P value
T0	2(2-2)	2(2-2)	1.000
T1	3(2-3)	2(2-2) *	0.000
T2	4(3-4)	3(3-3) *	0.000
T3	4(4-4)	4(4-4) *	0.010
T4	4(4-4)	4(4-4)	0.133
T5	4(4-4)	4(4-4)	0.317
T6	4(4-4)	4(4-4)	0.305
T7	4(4-4)	4(4-4)	0.642
T8	4(3.75-4)	4(4-4)	0.153
T9	4(3-4)	4(3-4)	0.624

Values are medians (interquartile range)

* $P < 0.05$ compared with the Control group

Table 4. Assessments of intraoperative events and evaluations in PACU

	Control Group	Intervention Group	P value
Lowest respiratory rate (breaths/min)	7.1±2.5	8.6±1.8*	0.000
Respiratory depression	24(80.0)	15(50.0) *	0.000
Incidences of			
oxygen supplementation by facial mask	24(80.0)	7(23.3) *	0.000
thrusting the jaw	11(36.7)	1(3.3) *	0.000
recall of events during surgery	0(0)	0(0)	1.000
Frequencies of			
body movements	0(0-0)	0(0-0)	0.000
additional rescue drug administrations	1(0.75-2)	1(0-2)	0.000
Recovery time (min)	22.9±9.6	16.0±3.0*	0.000
VAS score	0(0-1)	0(0-1)	0.000
Satisfaction score of patients	4(4-4)	4(4-4)	0.000
Satisfaction score of surgeons	4(4-4)	4(4-4)	0.000

Values are mean±SD or medians (interquartile range)

* $P < 0.05$ compared with the Control group

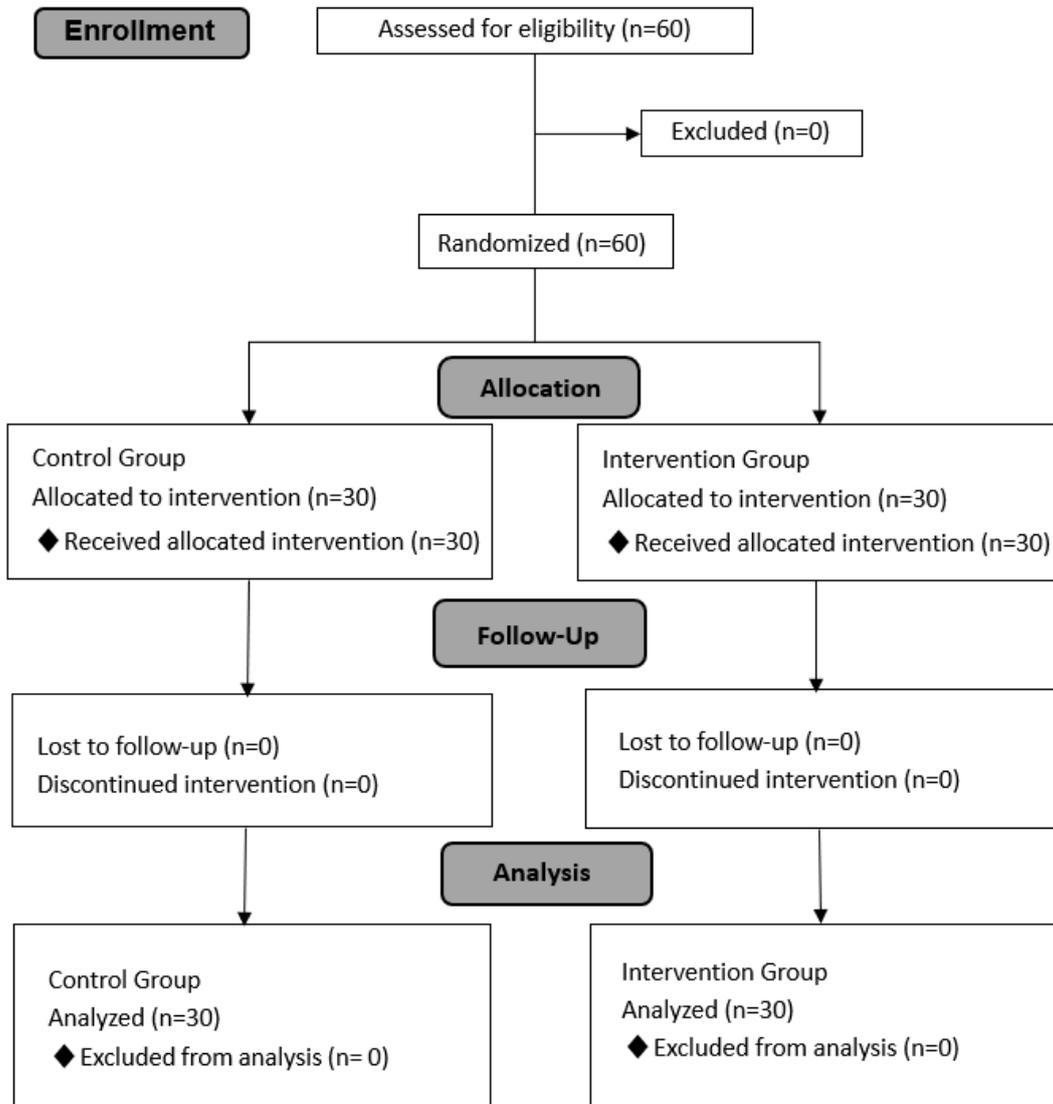


Figure1. A flow diagram shows the patients recruitment.

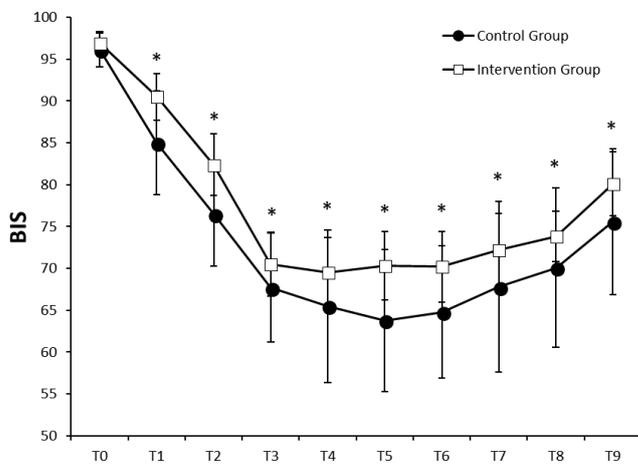


Figure 2. Changes in BIS. * $P < 0.05$ compared with the Control group.

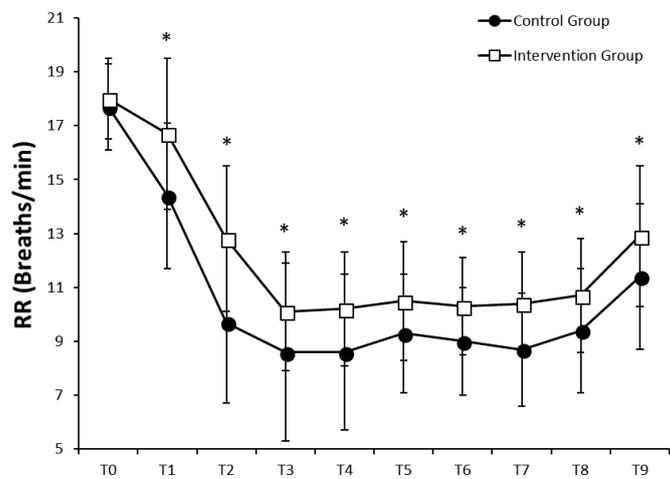
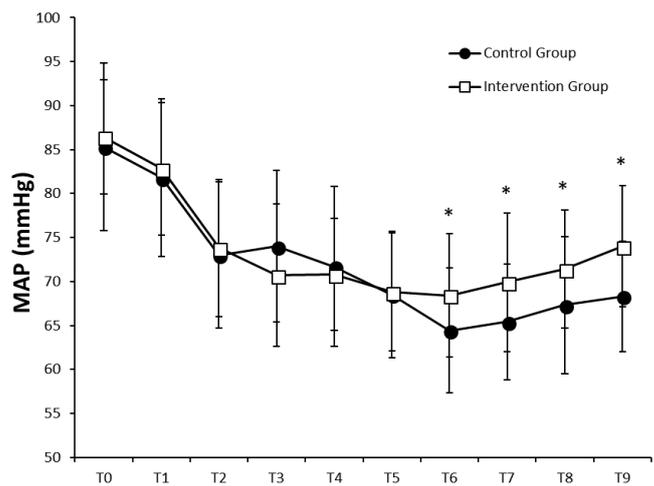
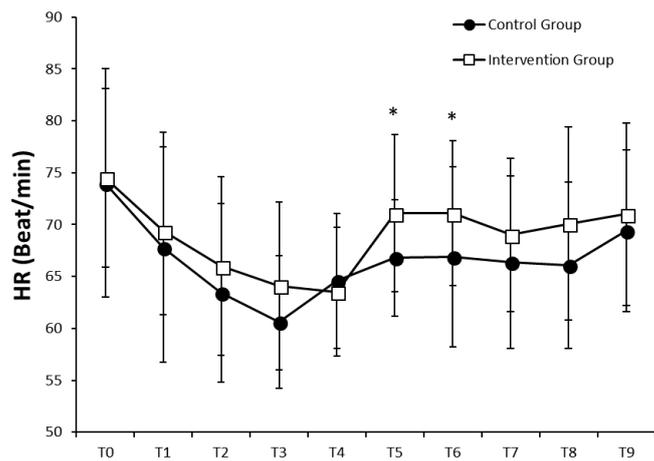


Figure 3. Changes in HR, MAP and RR. * $P < 0.05$ compared with the Control group.

Discussion

In this study, we found that although DEX infused with a loading dose over 15 min provided deeper sedation than DEX infused with a loading dose over 30 min, these two different DEX administrations could both be effectively applied in the surgery. In addition, DEX infused with a loading dose over 30 min resulted in more stable hemodynamics, less respiratory depression, and shorter recovery time for patients in sedative and analgesic anesthesia.

In order to achieve satisfactory sedation and analgesia, DEX is often used clinically in combination with other anesthetic drugs such as midazolam and opioids [9-11]. Midazolam reduces the incidence of recall of intraoperative events by producing anterograde amnesia [12]. Studies have shown that DEX combined with midazolam provided better sedation than midazolam alone in patients undergoing fiberoptic bronchoscopy [13]. The analgesic effect of DEX combined with opioids is beneficial in invasive operations. For example, a previous study demonstrated dexmedetomidine combined with remifentanyl provided better analgesia and higher satisfaction levels amongst surgeons than midazolam combined with remifentanyl in patients undergoing radiofrequency ablation for atrial fibrillation [8]. In our study, DEX was administered with midazolam and remifentanyl to produce sufficient sedation and analgesia for the surgery.

While enhancing the anesthetic effect, the combination of sedation and analgesic drugs may also increase the incidences of respiratory and circulatory depressions. Clinically, the safety of anesthesia can be improved by reducing the dose of drugs or adjusting the method of drug administration [14-16]. In our study, we extended the infusion time of DEX loading dose from 15 min to 30 min to delay the increment of DEX plasma concentration and attenuate the DEX peak plasma concentration. As shown in the present study, patients in the intervention group had a more gradual BIS change after DEX infusion. However, no differences were found between the groups in RSS from the beginning of local anesthesia to the end of surgery, intraoperative body movements, additional rescue drug administrations, recall of intraoperative events, pain scores in

PACU, or the satisfaction levels of patients and surgeons. Our results revealed that although the sedation depth in the intervention group was relatively shallow, this mode of DEX administration could achieve the sedation and analgesia required for the surgery. In a study of sedative and analgesic anesthesia, use of dexmedetomidine could significantly prolong postoperative recovery time [17]. In this study, the DEX plasma concentration of the intervention group after the loading dose infusion was theoretically lower than that of the control group. We found no differences in the surgery time between groups which lead to a better early postoperative recovery for patients in the intervention group.

With respect to hemodynamic stability, Bloor *et al.* [18] reported that the amount of DEX loading dose and the duration of administration affected the blood pressure, with blunting of the blood pressure by 23% 60 min after infusion of 1 µg/kg DEX over 2 min. The remifentanyl used in this study is a non-accumulative, ultra-short-acting opioid which allows faster recovery after anesthesia [19, 20]. We know from earlier studies that both remifentanyl and DEX reduce HR [21, 22]. We observed that the intervention group had higher MAP at time points from 30 min after local anesthesia to the end of surgery and higher HR at time points from the beginning of surgery to 30 min after local anesthesia, which indicated that prolonged DEX loading dose time contributed to more stable hemodynamics.

Though DEX provides sedation and analgesia without significant respiratory depression, respiratory changes needed to be measured in the case of drug combinations [23]. The depth of sedation can significantly affect patients' minute ventilation and RR [24]. In the present study, we found both groups showed respiratory depression during anesthesia. However, the intervention group had higher RR throughout the study and also had higher LRR, lower incidences of respiratory depression, oxygen supplementation by facial mask and thrusting the jaw. We concluded that prolonged DEX loading dose time reduced adverse respiratory reactions.

There are a few limitations to this study. The method of DEX administration in the control group is extensively applied in clinical practice. Though higher respiratory depression was observed in this group, the problem could be solved by oxygen supplementation with facial mask or thrusting the jaw. Before the study, we excluded

patients with known obesity or obstructive sleep apnea/hypopnea syndrome. For patients with a predictable risk of respiratory depression, further research is needed to identify the safety of this method of DEX administration.

Conclusion

In conclusion, our study demonstrated that DEX is an excellent drug when combined with other narcotic drugs in sedative and analgesic anesthesia. Prolonging the DEX loading dose infusion time from 15 min to 30 min can provide sufficient sedation during the surgery with more stable hemodynamics, as well as less respiratory adverse reactions.

Abbreviations

DEX: Dexmedetomidine

HR: Heart rate

MAP: Mean arterial pressure

RR: Respiratory rate

BIS: Bispectral index

RSS: Ramsy sedation scores

LRR: Lowest respiratory rates

PACU: Postanesthesia care unit

ASA: American Society of Anesthesiologists

BMI: Body mass index

ECG: Electrocardiogram

Acknowledgements

The authors thank the anesthetists and surgeons at our hospital who participated in this study. We would also like to acknowledge the professional assistance provided by Gilbert Xavier Gonzalez (Institute for Biomedical Sciences, Georgia State University, Atlanta, GA, USA) in reviewing and editing the English grammar in this manuscript.

Authors' Contributions

WPX, LXW and JHS designed and conducted the study, interpreted data and drafted the manuscript. WPX, DY, LW, JHL and YLS revised the manuscript and did the statistical analysis. XMD revised the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by Institutional Foundation of Plastic Surgery Hospital (No. Z2015005).

Availability of data and materials

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

Ethics approval and consent to participate

The study protocol was approved by Ethic Committee of Plastic Surgery Hospital, Chinese Academy of Medical Science (2016-12). All procedures were performed according to the Declaration of Helsinki and written conformed content was obtained from each patient prior to start. The trial was registered at the Chinese Clinical Trial Registry, registration number ChiCTR1900027958.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

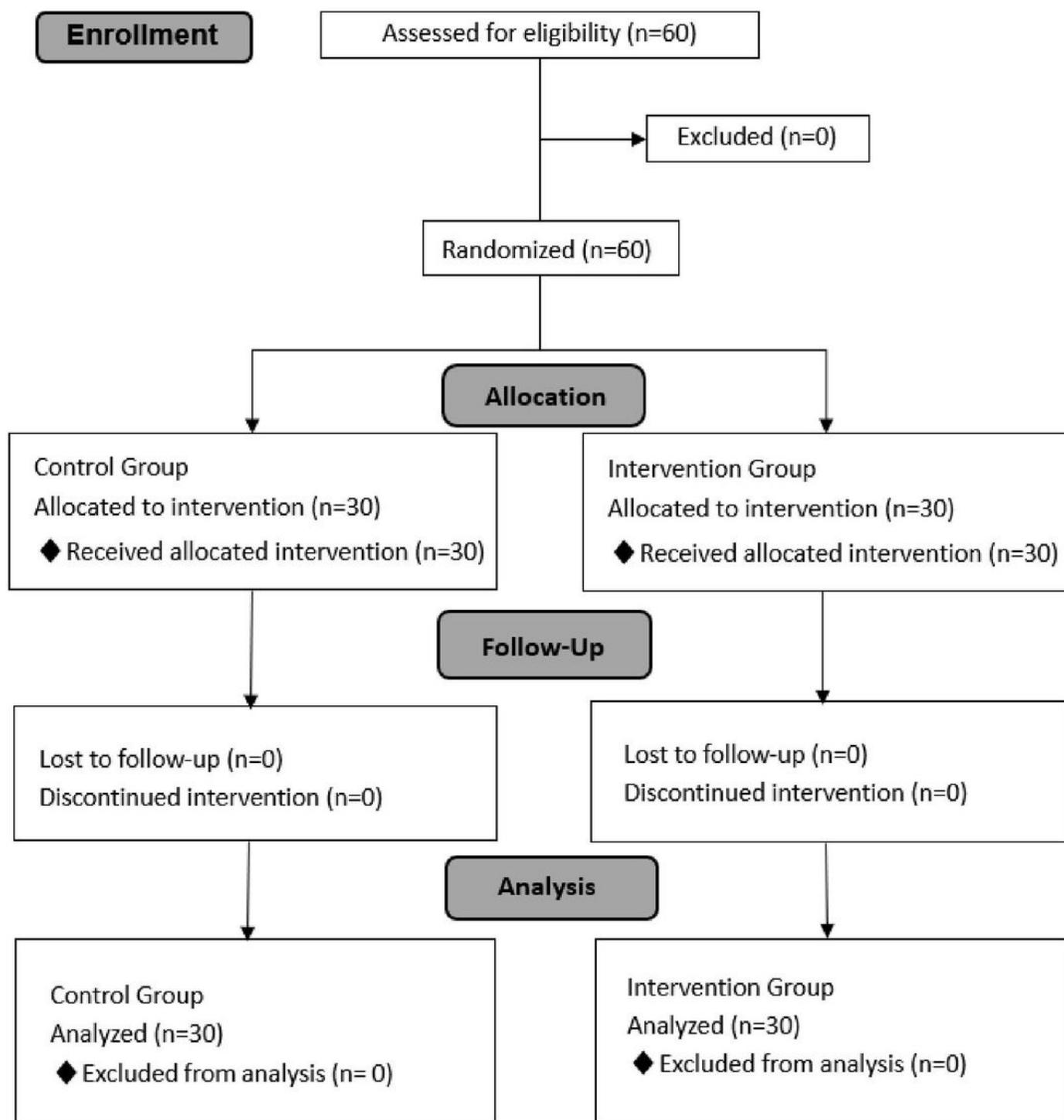


Figure 1

A flow diagram shows the patients recruitment.

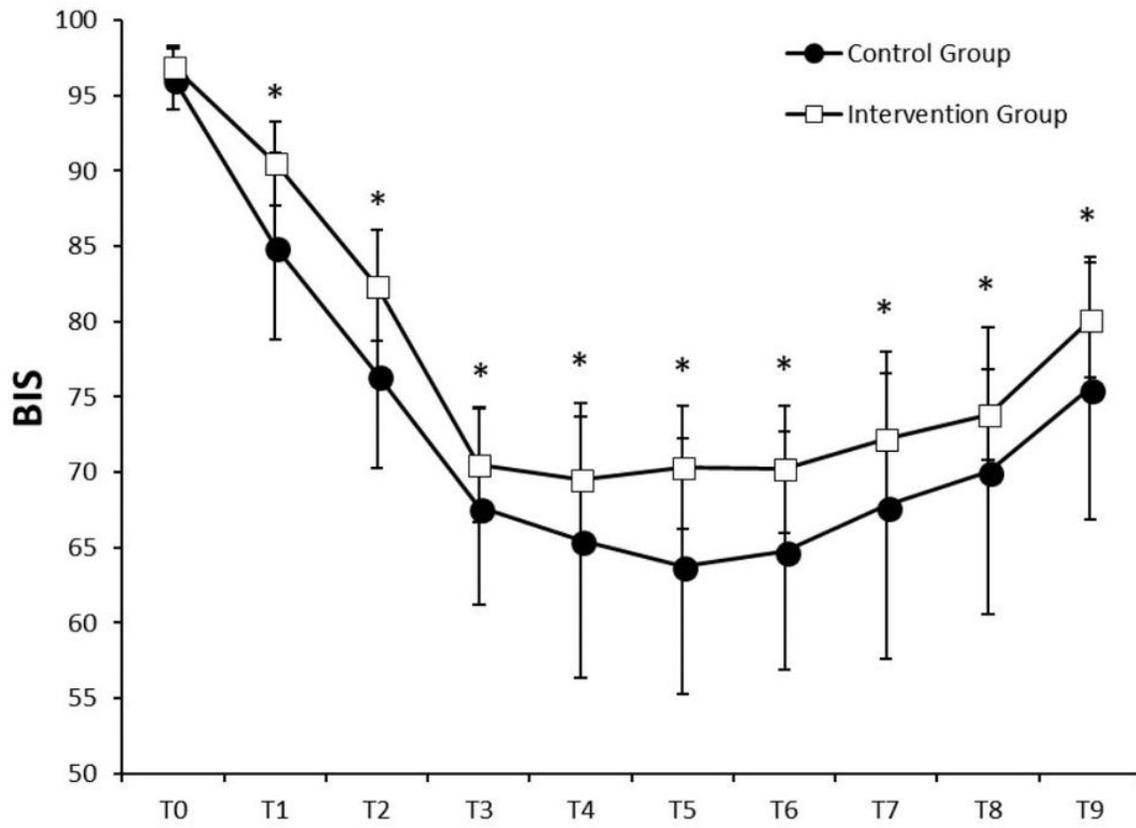


Figure 2

Changes in BIS. *P < 0.05 compared with the Control group.

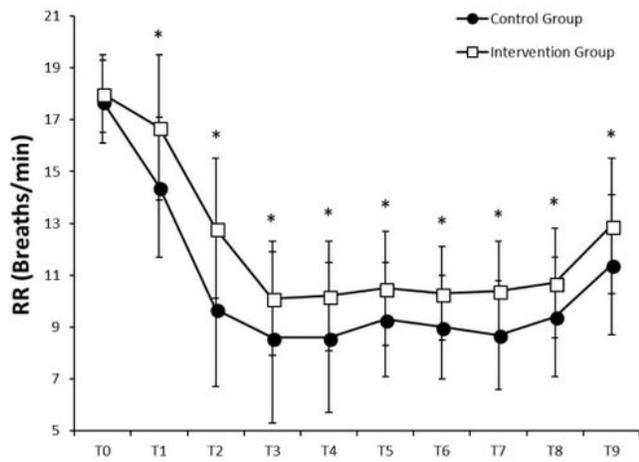
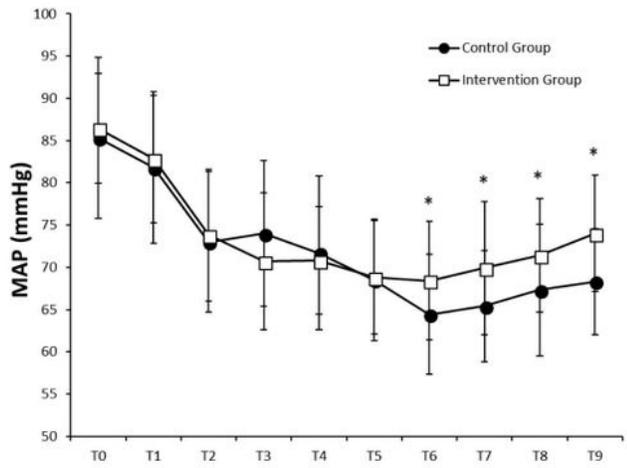
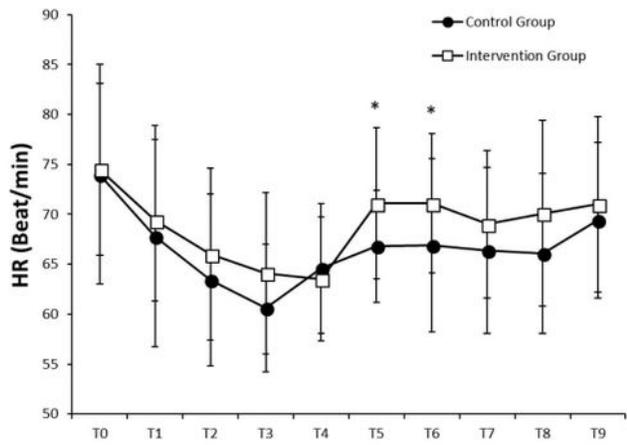


Figure 3

Changes in HR, MAP and RR. *P<0.05 compared with the Control group.