# Dexmedetomidine Versus Midazolam on Cough and Recovery Quality After Partial and Total Laryngectomy – a Randomized Controlled Trial

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**Research article**

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# Abstract

**Background** During emergence from anesthesia after partial and total laryngectomy, excessive airway reflex and systemic hypertension may lead to pneumoderm, hemorrhage or pneumothorax.

**Methods** ASA -  male adults undergoing elective laryngectomy were recruited and randomly allocated to receive either dexmedetomidine or midazolam. The primary outcome was incidence and severity of cough. Pulse oximetry ($SpO_2$ ), heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. Visual Analogue Scale (VAS) and Ramsay sedation scale (RSS) were recorded at the point of awareness and departure from PACU. Rescue analgesia required consumption, time of spontaneous breath recovery, duration of the PACU stay, incidence of adverse effects were also recorded.

**Results** The prevalence of no coughing was significantly higher in group D than group M while the patients were at the point of awake and departure. Compared with group M, there was significant decrease in HR, SBP and DBP in group D than group M, and $SpO_2$ was statistically significantly higher in group D than group M at the moment of laryngectomy. Pain scores were lower in group D than group M. The Ramsay score at awake in PACU was higher in group D than group M. There was no difference in time to spontaneous breathing recovery, duration of the PACU stayand incidence of adverse effects.

**Conclusions** Compared with midazolam, dexmedetomidine is an effective alternative to attenuate coughing and hemodynamic changes with low incidence of adverse events during emergence for partial and total laryngectomy.

**Trial registration**: NCT03918889, registered at clinicaltrials.gov, date of registration: March 28, 2019. Https://register.clinicaltrials.gov/prs/app/action/DownloadReceipt?uid=U0003V5T&ts=3&sid=S0008S19&cx=haixch


# Background

Laryngeal carcinoma is one of most common malignant tumors worldwide, which usually required head and neck surgery[1,2]. A study by the International Agency for Research on Cancer showed that 177,422 new laryngeal cancer cases occurred and resulted in 74,771 cancer-related deaths in 2018[3]. The treatment of laryngeal carcinoma has largely improved in past few years[4]. Partial and total laryngectomy is considered to be the most effective method except early-stage.

Patients with laryngeal carcinoma always have a history of long-term smoking, around 81% suffer from chronic obstructive pulmonary disease[5]. After surgery, air is no longer passing through the upper respiratory tract, without warming, humidifying and filtering, air directly cause irritation of trachea-bronchial mucosa. Tracheostomy tube is also a strong stimulus to trachea mucous. Coughing can lead to subcutaneous emphysema, pneumothorax, surgical bleeding, lung intercostal hernia[6]. Minimizing coughing and smooth emergence should be emphasized.

Dexmedetomidine is a highly selective alpha-2 adrenoceptor agonist, several studies have report dexmedetomidine may improve sympathicus, sedation, and analgesia without respiratory inhibition[7,8]. To the best of our knowledge, there have been no study compared recovery profiles between dexmedetomidine and midazolam in partial and total laryngectomy. Although the main drugs studied in our research are not commonly utilized during anesthesia for head and neck procedures, patients with tracheotomy after laryngeal carcinoma operation were chosen because of strong discomfort and restlessness caused by tracheotomy cannula, but tracheotomy completely guaranteed the safety of airway. The aim of our study was to compare the effect of dexmedetomidine with midazolam on hemodynamics and recovery quality after partial and total laryngectomy.

## Methods

# Study design

This study was approved by the hospital ethics committee of the Eye, Ear, Nose and Throat Hospital of Fudan University, Shanghai, China (2013005) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03918889, Principal investigator: Rui Xu, date of registration: March 28, 2019). We did a prospective, randomized, double-blind, single-center clinical trial in department of anesthesiology in the Eye, Ear, Nose and Throat Hospital of Fudan University. This manuscript adheres to the applicable CONSORT guidelines.

Patients were randomly allocated to either group dexmedetomidine (group D) (n = 43) or group midazolam (group M) (n = 43). Randomized group allocation was performed using a computerized randomization table created by one staff member who was not involved in the patients' anesthesia or recovery care. The randomization result was kept sealed in an envelope, only the nurse who prepared the anesthetics could open the envelope in order to prepare allocated drug. A total of 83 medical records were analyzed, 43 from group D and 40 from group M. The patients, the nurse in post anesthesia care unit (PACU), and attending anesthesiologist were blinded to the study medicine administration.

# Inclusion Criteria

We enrolled 86 adult patients with American Society of Anesthesiologist physical status (ASA) Ⅱ or Ⅲ, aged 25–70 years, male, scheduled for partial or total laryngectomy.

# Exclusion Criteria

Patients with cardiac disease, neuropsychiatric diseases, pharyngeal paraganglioma, uncontrolled hypertension (i.e., systolic blood pressure > 160 mmHg or diastolic blood pressure > 90 mmHg), take β-adrenoreceptor blockers, long-term (> 6 months) abuse of alcohol, opioids or sedative-hypnotic drugs,

dexmedetomidine or midazolam allergies, undergo awake fiberoptic intubation, operation time shorter than 1 h or longer than 4 h, patient who had tracheotomy history were excluded.

# Anesthesia

Drugs including sedative, analgesic, antiemetic and anti-itching drugs were not given before operation. After arrived at operation room, electrocardiogram, pulse oximetry, blood pressure, bispectral index, end-tidal carbon dioxide and temperature were continuously monitored and recorded. General anesthesia was induced with sufentanil 0.2 μg/kg, propofol 2.5 mg/kg, after confirmation of adequate muscle relaxation with the administration of cisatracurium 0.2 mg/kg iv, an endotracheal tube with internal diameter of 7 mm was inserted into the trachea. Endotracheal tube cuff pressure was maintained at 25 $cmH_2O$ measured using a calibrated handheld Portex Cuff Inflator Pressure Gauge (Portex Limited, Hythe, Kent, UK). Prior to the start of surgery, sufentanil 0.1 μg/kg was given. Either dexmedetomidine (Precedex; Henrui Pharmaceutical, China) (group D, n = 43) infusion at 0.5 μg/kg for 10 min before tracheotomy, then adjusted to 0.3 μg/kg/h or midazolam (Midazuolun injection; Enhua Pharmaceutical, China) (group M, n = 43) infusion at 0.05 mg/kg ten minutes before tracheotomy, then adjusted to 0.02 mg/kg/h was administered in a blind mode. Anesthesia was maintained with 1-1.3 minimum alveolar concentration end-tidal concentration of sevoflurane in 30% oxygen/air mixture to keep bispectral index between 45 and 55. The maintenance infusion rate of cisatracurium is 1-1.5 μg/kg/min and tmaintenance infusion rate of sufentanil was 0.002 μg/kg/min according to clinical needs. Granisetron 6 mg was administered at the end of surgery for prevention of postoperative nausea and vomiting (PONV). Endotracheal secretions were removed before tracheostomy tube insertion. Topical tetracaine hydrochloride gel was applied to the tracheostomy tube in order to enhance toleration.

After surgical procedures were finished, sevoflurane was discontinued, 100% oxygen was administered at 6 l/min and then patients were transferred to PACU. Neostigmine 0.04 mg/kg and atropine 0.02 mg/kg were given to reverse residual neuromuscular block. After spontaneous ventilation returned, confirmation patient had fully recovered from muscle relaxation and after patients opened eyes, patients were weaned from mechanical ventilation. Nurses who assessed subjects were blinded to the medicine intervention. If there was any adverse event, an attending anesthesiologist managed it. In case of bradycardia (heart rate (HR) < 45 beats/min), 0.5 mg atropine was administered, if systolic blood pressure (SBP) decreased to less than 90 mmHg, ephedrine 6 mg was used.

Cough grading was based on modified 4-point Minogue scale. Grade 1 equates to no cough; grade 2 (mild) represents coughing once or twice; grade 3 (moderate) means fewer than 4 non-sustained coughs lasting 1–2 s each or overall coughing lasting less than 5 s; grade 4 (severe) was at least 4 coughs lasting at least 2 s, or overall coughing duration was more than 5s[9]. The patients' level of sedation was assessed by ramsay sedation scale (RSS):1 = the patient is anxious and restless or agitated, or both; 2 = the patient is cooperative, tranquil, and oriented; 3 = the patient responds to commands only; 4 = the patient exhibits a brisk response to a loud auditory stimuli or a light glabellar tap; 5 = the patient exhibits

a sluggish response to a loud auditory stimulus or a light glabellar tap; 6 = the patient exhibits no response[10]. In addition, the nurse also assessed postoperative pain score by visual analogue scale (VAS) (0–10; 0 = no pain, 10 = worst pain). If pain score was above 5, sufentanil 0.1 μg/kg was given to patients immediately as rescue analgesic, consumption of analgesics was recorded.

HR, SBP, diastolic blood pressure(DBP) and pulse oximetry($SpO_2$) were recorded before induction($T_1$), after drug administration($T_2$), after intubation($T_3$), after medicine intervention($T_4$), at moment of laryngectomy($T_5$), completion of surgery($T_6$), at the point of awareness($T_7$), at departure from PACU($T_8$), 2 h after surgery($T_9$), 24 h after surgery($T_{10}$), 48 h after surgery($T_{11}$). Duration of surgery, respiratory recovery time, duration of PACU stay was also recorded. Incidence of adverse events including bradycardia, hypotension (< 30% decrease from baseline), hypertension(> 30% increase from baseline), vomiting, pale lip, delirium, subcutaneous emphysema, hematoma were noted by a nurse who was blinded to medicine intervention. The incidence of pneumonia in the 72 hours after surgery was also collected.

# Statistical Analysis

The primary endpoint was incidence and severity of cough. The secondary outcome measures were hemodynamic responses, postoperative pain scores, sedation scores, respiratory recovery time, duration of PACU stay, and incidence of adverse events.

PASS15 was used to calculate sample size. On basis of preliminary study, incidence of no cough in group M was about 65%, and group D was about 25% higher than group M. The proportion in group D is assumed to be 0.65 under the null hypothesis and 0.90 under alternative hypothesis. The proportion in group M is 0.65. The test statistic used is one-sided Z-Test with unpooled variance. The significance level of the test is 0.025. Group sample sizes of 40 in group D and 40 in group M achieve 80% power to detect a difference between the group proportions of 0.25. Assuming a dropout rate of 8%, final sample size was determined to be 43 patients each group, with a power of 80% and an alpha level of 0.05.

The t test was used for between-group comparisons of HR, SBP, DBP, and $SpO_2$. Repeated-measures ANOVA was used for within-group comparisons. The $\chi^2$ test or the Fisher exact test was used to analyze coughing severity, sedation, pain scores and adverse events. A p-value of 0.05 or less was considered statistically significant.

## Results

# Baseline characteristics

86 patients were recruited (Fig. 1) between May 2019 and September 2019. Two patients in group M required voice reconstruction and quit from the study; one patient in group M was excluded as he underwent a second surgery because of excessive incisional bleeding. Thus, 83 patients completed this

study (43 from group D, 40 from group M). There were no significant differences between two groups in terms of baseline clinical characteristics (p > 0.05, supplemental table 1).

**Supplemental table 1. Demographics and baseline variables of patients in two groups.**

# The Incidence And Severity Of Coughing

The prevalence of no coughing was significantly higher in group D than group M while patients were at point of awake (*88% [38] vs 65%* [26], *p = 0.018*) and departure (*100% [40] vs 65%* [28], *p = 0.009*) (Table 1). No patient in group D experienced severe coughing, whereas 3 patients in group M. The incidence of mild cough was significantly lower in group D than group M (*14%* [6] *vs 40%* [16] *of patients, respectively; p = 0.015*). Patients with grades 3 and 4 will be categorized as “moderate to severe”, the incidence of “moderate to severe” cough was significantly higher in group M than group D (*5%* [2] *vs 40%* [16] *of patients, respectively; p = 0.012*).

Table 1
The incidence and severity of coughing in PACU.

| No Cough | | Mild Cough | | Moderate Cough | | Severe Cough | |
|---|---|---|---|---|---|---|---|
| Awake | Departure | Awake | Departure | Awake | Departure | Awake | Departure |
| Group D | 38* | 40** | 3 | 3 | 2[&] | 0 | 0 | 0 |
| Group M | 26 | 28 | 7 | 9 | 5 | 2 | 2 | 1 |

*p = 0.018 vs Group M (awake).

**p = 0.009 vs Group M (departure).

Moderate + Severe, [&]p = 0.012 vs Group M.

# Perioperative Hemodynamic Changes

Compared with group M, there was significant decrease in HR at $T_3$, $T_4$,$T_5$, $T_6$, and $T_7$ compared with values in group D. HR in group M was significantly increased at moment of intubation, at moment of laryngectomy compared with values before anesthesia ( Fig. 2A).

As is shown in Fig. 2B and Fig. 2C, SBP(*131.98 vs 120.33*, *p = 0.005*) and DBP(*82.88 vs 76.98*, *p = 0.042*) was significantly increased at moment of laryngectomy in group M than group D. Compared with before anesthesia values, SBP was significantly lower at the moment of other points (*p < 0.01*) in group D. Compared with before induction values, SBP was significantly lower in group M after $T_2$, $T_3$, $T_4$,$T_5$, $T_6$ (*p < 0.01*), but no significant difference at point of awareness and departure from PACU (*p 0.05*).

$SpO_2$ was statistically significantly higher in group D than group M at moment of laryngectomy (*97.77vs96.60, P = 0.040*). However, at 2 h after surgery, $SpO_2$ was significantly higher in group M than group D(*96.14vs97.03, p = 0.041*) (Fig. 2D). Desaturation ($SpO_2$ < 92%) was observed in five patients in group M but no patient in group D at the point of laryngectomy (p = 0.029) [Supplemental table 2]. The overall incidence of desaturation was lower in group D than group M (*20[47%] vs 29 [72%], respectively; p = 0.029)*[ Supplemental table 2].

# Supplemental Table 2. Oxygen Desaturation (spo < 92%)

There was no significant difference in time to respiratory recovery and duration of PACU stay between two groups [Table 2]. As shown in Table 3, RSS at awake in PACU was higher in group D than group M*(1.98 vs1.80, p = 0.025)*.

Table 2
Recovery Profiles.

| Time | Group D(n = 43) | Group M(n = 40) | P |
|---|---|---|---|
| Recovery time(min) | 26.6±12.1 | 28.5±12.3 | 0.475 |
| Awake time(min) | 46.5±16.0 | 46.2±14.7 | 0.938 |
| Values are mean ± SD or number. | | | |

Table 3
Ramsay score.

| Ramsay score(1/2/3) | Group D(n = 43) | Group M(n = 40) | P |
|---|---|---|---|
| Awake | 1/42/0 | 8/32/0 | 0.025 |
| Departure | 1/42/0 | 1/39/0 | 1.00 |
| 2 h after surgery | 0/43/0 | 1/38/1 | 0.332 |
| Grade of sedation, 1 = anxious and restless or agitated, 2 = cooperative, tranquil, and oriented, 3 = responds to commands only. | | | |

# Postoperative Pain Score

There is no significant difference in postoperative pain score between two groups at point of awareness. But postoperative pain score was significantly lower in group D than group M at moment of departure(*1.21 vs 2, p < 0.001*). The requirement for rescue analgesics was significantly lower in group D than group M (*4 vs 13, p = 0.013*) [Table 4].

Table 4
Pain scores and postoperative requirement for rescue analgesics at PACU.

| | Group D(n = 43) | Group M(n = 40) | P |
|---|---|---|---|
| VAS score ($T_7$) | 1.58±1.56 | 2.03±1.97 | 0.261 |
| VAS score ($T_8$) | 1.21±0.94 | 2.00±1.96 | 0.024 |
| Rescue analgesics(n) | 4 | 13 | 0.013 |
| Values are mean ± SD or number. | | | |

# Adverse Events

The incidence of postoperative complications are presented in supplemental table 3. There was no significant difference between two groups. Vomiting was noted in 7 patients in group D and 12 in group M. Hypertension was observed in 1 patient in each group. Pale lips was observed in 2 patients in group D, severe bradycardia in 1 patient in group D, delirium was reported in 2 patients in group M, subcutaneous emphysema in 1 patient in group M, while re-exploration of operation site for hematoma was observed in 1 patient in group M. Postoperative pneumonia was noted in 1 patient in group M. During the operation, vasopressor was used in 18 patients in group D and 11 in group M.

# Discussion

This study showed dexmedetomidine provided adequate and satisfactory coughing suppression, stable hemodynamics and recovery quality for patients undergoing partial and total laryngectomy.

64% patients suffer coughing after total laryngectomy, and patients undergo partial laryngectomy always suffer higher frequency of coughing[11]. Coughing after laryngectomy always related to airway secretions or presence of tracheostomy tube, we used a suction to remove oral and airway secretions before tube insertion. And we used topical tetracaine hydrochloride gel to tracheostomy tube to reduce peripheral nervous perception of tube stimulating. Our results show prevalence of no coughing was significantly higher in group D than group M. No patient in group D experienced severe coughing. This result is consistent with previous study that dexmedetomidine is effective in attenuating air-way reflex to tracheal extubation[12]. Several pharmacological methods has been reported could decrease coughing including lidocaine and opioid. Recently, a systematic review has been sponsored to investigate optimal pharmacological methods for reducing coughing after general anesthesia[13]. Opioid such as remifentanil and fentanyl are common for preventing cough, but opioid drugs can produce undesirable adverse events, such as respiratory depression, delayed awakening, and PONV. In our research there were no significant differences in time to respiratory recovery and duration of PACU stay between two groups, also the dose of dexmedetomidine did not appear to induce respiratory depression.

Blunting cardiovascular response can decrease incidence of complications. Compared with group M, there was significant decrease in HR, SBP and DBP at the moment of laryngectomy. We did not use combining dexmedetomidine and remifentanil for possibility of delayed awakening[14]. Dexmedetomidine can reduce release of norepinephrine, result in decreased catecholamine release from nerve terminal with a resultant central sympatholytic effect leading to decreased heart rate and blood pressure[15]. However, dexmedetomidine also has some disadvantages including inducing bradycardia and hypotension in old patients. Severe bradycardia was observed in 1 patient in group D. Vasopressor was used in 18 patients in group D and 11 in group M. Hypotension and bradycardia occur more commonly with the initial loading dose in group D. Previous research has reported that midazolam had no significant effects on sympathetic tone but slightly decreased blood pressure about 10 minutes due to decreased systemic vascular resistance and myocardial contractility[16,17]. We speculated lower dose of dexmedetomidine maybe more appropriated to elderly patients. $SpO_2$ was significantly higher in group D than group M at moment of laryngectomy. This may be attributed to decreased HR induced lower oxygen consumption. Animal experiments have reported dexmedetomidine preconditioning exerts cardioprotective effects against hypoxia injury and can improve perioperative hypoxemia[18,19].

Emergence agitation can result in cardiovascular instability, decreased venous return to increased intracranial pressure, decreased functional residual capacity, wound dehiscence and hemorrhage[20]. Midazolam is an effective sedative, anxiolytic which provides anterograde amnesia. But it has been reported there is a high risk of drug accumulation and delirium when used midazolam in patients with liver dysfunction[21]. In our research, delirium was observed in 2 patients in group M, but all relieved within 24 hours. We found satisfactory sedation with dexmedetomidine. Dexmedetomidine exhibits a high specificity for $\alpha_2$ vs $\alpha_1$ receptor[22], which produces unique characteristic of sedation similar to normal sleep. Dexmedetomidine has been reported used for long-term sedation during mechanical ventilation in critically ill patients during intensive care unit and for decreasing patient agitation during PACU [23]. Our results also confirmed dexmedetomidine maybe an effective agent for sedation in partial and total laryngectomy.

Partial and total laryngectomy is associated with a high level of pain[24]. Our results show that postoperative pain score and requirement for rescue analgesics was significantly lower in group D than group M. The analgesic efficacy of dexmedetomidine is still controversial[25]. The analgesic mechanism of dexmedetomidine is a subject remaining to be further studied.

Although there were more adverse events in group M compared with group D, but the difference was not statistically significant. Insertion of stomach tube is also a risk factor of PONV, all patients retained stomach tube in our study. Patients who breath via a tracheostomy cannot make use of their glottis and are at a mechanical disadvantage [26]. Preservation of cough reflex is mandatory to prevent pulmonary complications[27]. No patient undergoed pneumonia in group D. The finding that postoperative pneumonia did not differ between two groups suggests dexmedetomidine did not associate with postoperative pulmonary infections.

There were several limitations. The major limitation was we investigate only one dose of dexmedetomidine, so we can not tell most optimal dose. Second, the sample size was relatively small, future multicenter studies comprising larger sample sizes are needed. Third, we did not include patients with bilateral cervical lymph node dissection, since the wounds are always larger, so our results were not suitable for these patients. Fourth, we did not include patients older than 70, in Europe and North America, approximately 30% of all head and neck cancer patients are aged over 70 years[28]. Finally, a number of potential sources of heterogeneity including the fitness of the patient's trachea and tracheostomy tube, surgery performed by different surgeons.

## Conclusions

In conclusion, intraoperative infusions of dexmedetomidine has its own advantages including providing blunt airway reflex, good sedative strategy and stable hemodynamics with analgesia effect, low risk of adverse events. Using dexmedetomidine improved outcome, alleviated patient discomfort to tracheostomy tube and allowed for a smooth emergence from anesthesia.

## List Of Abbreviations

group dexmedetomidine (group D)

group midazolam (group M)

postanesthesia care unit (PACU)

Pulse oximetry ($SpO_2$ )

heart rate(HR)

systolic blood pressure (SBP)

diastolic blood pressure (DBP)

Visual Analogue Scale (VAS)

Ramsay sedation scale (RSS)

American Society of Anesthesiologist physical status (ASA)

postoperative nausea and vomiting (PONV)

## Declarations

# Ethics approval and consent to participate

This study was approved by the hospital ethics committee of the Eye, Ear, Nose and Throat Hospital of Fudan University, Shanghai, China (2013005) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03918889, Principal investigator: Rui Xu, date of registration: March 28, 2019).

### Consent to publish

Informed consent was obtained and the consent form was signed by the parents of each participant.

### Availability of data and materials

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

### Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

RX helped to design the study, conduct the study, analyze the data, and write the manuscript. YZ helped to design the study, conduct the study, analyze the data. YL helped to design the study, conduct the study, analyze the data, and write the manuscript. LWX designed the study, analyzed the data, and wrote the manuscript. JJE designed the study, conducted the study, and analyzed the data. All authors have read and approved the manuscript.

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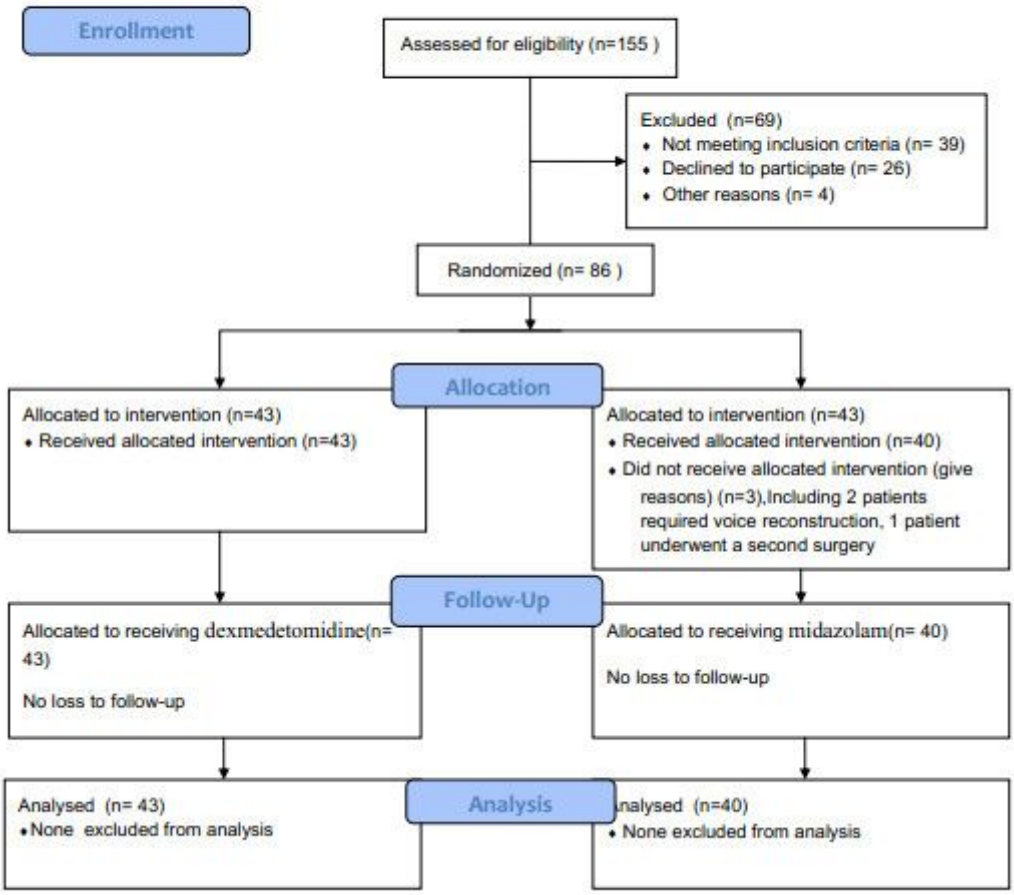
# Figures

**Fig 1. Consort flow diagram.**




## Figure 1

Consort flow diagram.

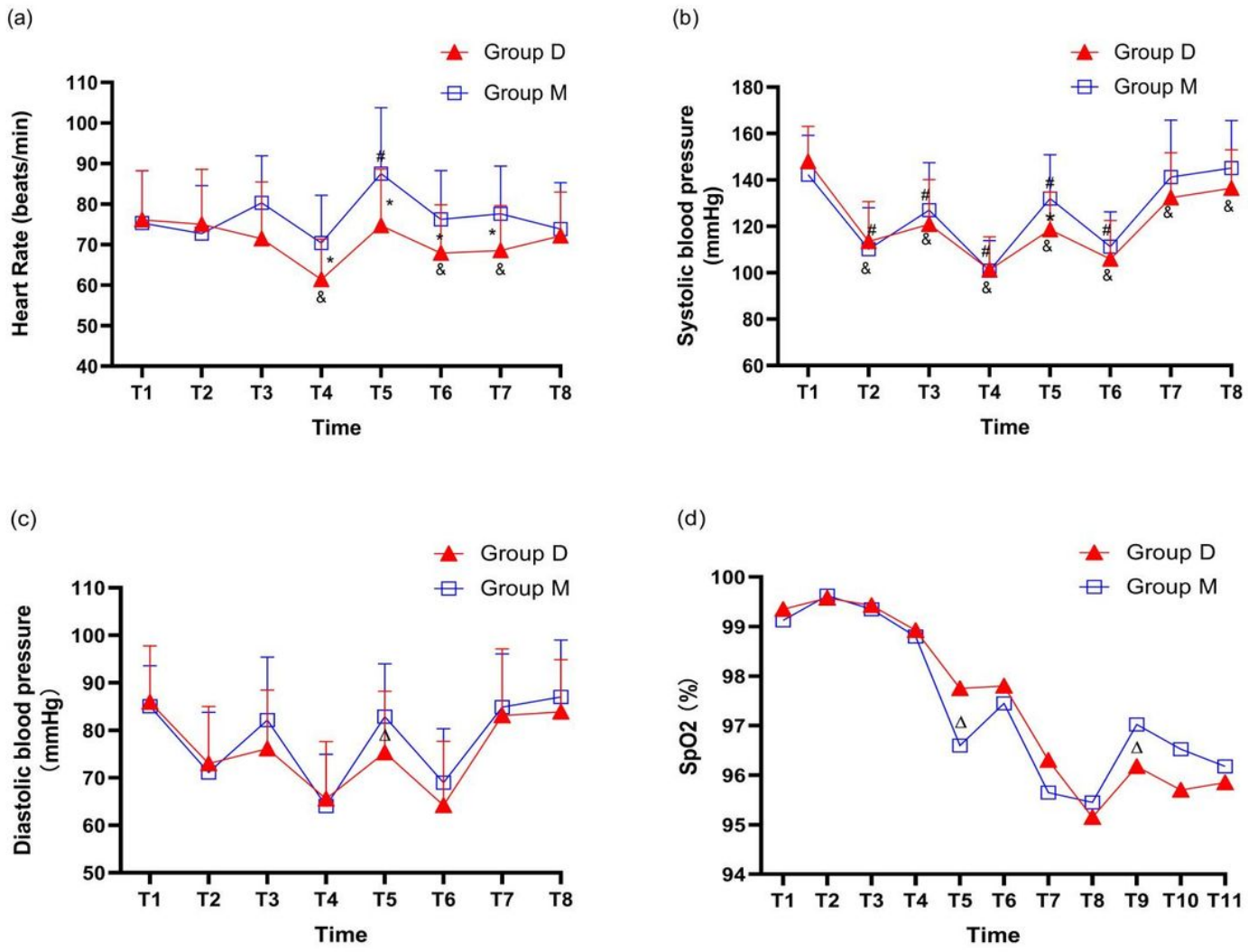



**Figure 2**

Hemodynamic changes. (A) Comparison of mean HR. (B) Comparison of mean SBP. (C) Comparison of mean DBP. (D) Comparison of mean SpO2. *P<0.01; &P<0.01 group D versus T1; #P<0.01 group M versus T1; ΔP<0.05.

# Supplementary Files

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

- CONSORT2010Checklist1.doc
- Supplementaltable3.docx
- Supplementaltable2.docx
- Supplementaltable1.docx