

# Sufentanil EC50 for Endotracheal Intubation with Aerosol Inhalation of Lidocaine

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## Research article

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# Abstract

**Background:** Nebulized lidocaine combined with opioid drugs was a classical implementation for awake intubation or rigid bronchoscopy. In this study, aerosol inhalation of carbonated lidocaine combined with sufentanil was accomplished prior to induction of anesthesia, to dig out whether the dosage of sufentanil could less or not, and the sufentanil EC50 for endotracheal intubation under these drugs combination.

**Methods:** Intravenous injection of sufentanil starting at 0.5 µg/kg. Then sufentanil dosages were increased/decreased (step-size 0.05 µg/kg for sufentanil) using Dixon and Massey up and down method in the next patient depending upon previous patient's response within 3 min after intubation. The observation was terminated after 8 reflexes. The hemodynamic indexes were recorded.

**Results:** The EC50 and EC95 of sufentanil with aerosol inhalation of lidocaine for endotracheal intubation was found to be 0.232 µg/kg (95% CI: 0.187-0.270 µg/kg) and 0.447 µg/kg (95% CI: 0.364-0.703 µg/kg). 55.88% out of 34 patients showed hemodynamic index change <20% of baseline during endotracheal intubation.

**Conclusion:** Aerosol inhalation of lidocaine could reduce the dosage of sufentanil for endotracheal intubation. The advantages in lidocaine inhalation for airway anesthesia by ultrasonic atomizer could be recommended in patients who need more stable hemodynamic changes.

*Trial registration: Chinese Registry of Central Trial, ChiCTR-IOR-17014198. Registered 28 December 2017, <http://www.chictr.org.cn/showprojen.aspx?proj=22301>*

## Background

Endotracheal intubation is a routine procedure in clinical general anesthesia, but complicated. The placement of laryngoscope and endotracheal tube may irritate the glottis and trachea, which results in hemodynamic changes, assumed to be a reflex sympathetic reaction [1]

There are several ways to attenuate the adverse hemodynamics fluctuations during laryngoscopy placement and tracheal intubation, reducing the stress response of intubation, such as enhancing the depth of anesthesia with high-dose opioids, airway surface anesthesia with local anesthetic, or preventing the adverse cardiovascular events with negative inotropic drugs and antihypertensive drugs. High-dose opioids caused side effects like respiratory depression, interference with the immune system and decrease in intestinal motility. And then opioids have been reported to increase cancer recurrence after surgery by inducing immunosuppression through their effects on natural killer cell activity [2]. Moreover, cardiovascular drugs which preventing the adverse of cardiovascular events are high risk factors for cardiovascular and cerebrovascular diseases in elderly patients [3, 4], which limits the clinical application.

Lidocaine, as an anti-inflammatory, anesthetic and antiarrhythmic drug, is often used for airway surface anesthesia or spinal anesthesia. It has been reported that both 2% and 4% lidocaine administered topically by a spray-as-you-go technique could provide clinically acceptable intubating conditions for awake fiberoptic orotracheal intubation in sedated patients with a difficult airway. It takes effect in 5 minutes and reached the peak in about 8 minutes. Nebulized lidocaine was used as a premedication to general anesthesia in spontaneously breathing pediatric patients undergoing bronchoscopy and in the treatment of intractable cough [5, 6].

There are some advantages in lidocaine inhalation for airway anesthesia by ultrasonic atomizer as its simplicity and convenience. It reported that cardiovascular responses were inhibited by 0.5 µg/kg to 1.0 µg/kg of sufentanil effectively [7, 8]. We speculated that the combined use of aerosol inhalation of carbonated lidocaine was expected to reduce the amount of sufentanil used. Hence, in this study, we aimed to dig out sufentanil EC50 for endotracheal intubation with aerosol inhalation of carbonated lidocaine by ultrasonic atomizer.

## Methods

### Inclusion and exclusion criteria

This was a single centre, prospective, double blind clinical trial to determine the EC50 of sufentanil for endotracheal intubation with aerosol inhalation of nebulized lidocaine.

Testing was performed in Tongji hospital. Patients, American Society of Anesthesiology (ASA) grade I or II, age 18–70 years, were scheduled to undergo elective surgery with no liver and renal dysfunction and no cardiovascular disease. The one with a history of local anesthetic allergy, oral and otolaryngologic lesions or surgical history, and COPD (chronic obstructive pulmonary disease) was excluded. Patients participating in other clinical trials or researchers were considered excluded as well. All patients were given informed consent. They were evaluated preoperatively 1 day prior to surgery. A complete history of present and past illness was taken, general physical examination and systemic examination was conducted to assess the fitness for proposed surgical procedure under general anaesthesia. Premedication was not prescribed to any patients.

### Study Protocol

40 Patients were screened for eligibility, who monitored by blood pressure (BP), pulse (P), electrocardiogram (ECG), SpO<sub>2</sub>, Nacrotrend values and muscle relaxant monitoring (train of four, TOF) during perioperative period. After intravenous cannulation, the radial artery puncture and catheter under local anesthesia was established for direct arterial blood pressure (ABP) monitoring. Aerosol inhalation of 4 mg/kg carbonated lidocaine by the ultrasonic atomizer(YUWELL,402B)was accomplished prior to induction of anesthesia. Waited 5 min for lidocaine to take effect. Then intravenous of anesthesia was achieved with propofol TCI (according to Nacrotrend monitoring anesthesia depth), rapid induction of

rocuronium 0.9 mg/kg, intravenous injection of sufentanil starting at 0.5 µg/kg. Until Nacrotrend monitoring value to 40, and monitoring TOF value to 0, the experienced anesthesiologist implemented endotracheal intubation using the general laryngoscope. Propofol and remifentanyl were continuous intravenous pumping, and intermittent injection of rocuronium was to maintain muscle loose.

The Dixon's up and down method was adopted [9], and intravenous injection of sufentanil starting at 0.5 µg/kg. Then sufentanil dosages were increased/decreased (step-size 0.05 µg/kg for sufentanil) using Dixon and Massey up and down method in the next patient depending upon previous patient's response within 3 min after intubation. The observation was terminated after 8 reflexes. Endotracheal intubation was performed and scored by the same attending physician.

The time points needed record were prior to the aerosol lidocaine inhalation (T0), after the aerosol lidocaine inhalation (T1), after intravenous induction (T2), at the time point of endotracheal intubation (T3), and 1 min (T4), 2 min (T5), 3 min (T6) after endotracheal intubation. The patients' HR, P, BP, SpO<sub>2</sub>, and Nacrotrend values were collected.

## Blinding

The observations in response to endotracheal intubation was recorded by an independent anesthetist. Monitor screen was applied between the anesthetist for observations and the anesthetist attempting endotracheal intubation. The patient and the anesthetists were not aware of the intravenous dosage of sufentanil.

## Outcome Measures

The primary outcome was effective concentration (EC<sub>50</sub>) of sufentanil causing "Hemodynamic index change < 20% of baseline" during endotracheal intubation in 50% of study population. Adverse events to circulation (HR, BP) were noted as secondary outcomes.

## Statistical analysis

Statistical analysis was performed using Excel 2007 (Microsoft, Redmond, WA, USA) and SPSS version 15.0 software (IBM, Armonk, NY, USA). Patients' characteristics were presented as mean (SD) or absolute numbers (percentages). Continuous variables were analyzed by t-test and categorical variables were analyzed by  $\chi^2$  test. Sufentanil EC<sub>50</sub> was calculated by modified Dixon's up and down method (MDUDM) [10]. The mean of mid-point of all unsuccessful/successful pairs was used to determine EC<sub>50</sub> using Dixon and Massey's up and down method. Dose-response curve for EC<sub>50</sub> with 95% confidence intervals (CI) were determined using probit regression analysis. Sample size was calculated based on the fact that a minimum of 8 crossover pairs were required for the analysis using modified Dixon and Massey's up and

down method. The Pearson correlation analysis was used to study the correlation between patient's characteristics and response to endotracheal intubation.

## Results

We assessed 40 patients for eligibility. Out of which 36 eligible patients were recruited in the study (Fig. 1). 2 patients were excluded from the study. Demographic characteristics of study population were presented in Table 1.

Table 1  
Demographic data of study population

<b>Male/Female</b>	<b>16/18</b>
ASA I/II	29/5
Age (y)	47.35 ± 11.87
Height (cm)	162.65 ± 7.08
Bodyweight (kg)	58.15 ± 6.76
BMI	22.00 ± 2.32
Mallampati Grade I/II	31/3
Values are presented as mean ± SD or absolute numbers.	

The EC50 and EC95 of sufentanil with aerosol inhalation of lidocaine for endotracheal intubation was found to be 0.232 µg/kg (95% CI: 0.187–0.270 µg/kg) and 0.447 µg/kg (95% CI: 0.364–0.703 µg/kg). The intravenous dosage of sufentanil-response data of endotracheal intubation for each patient obtained by the up-down method (Fig. 2). The concentration response curve of sufentanil plotted from probit analysis of intravenous dosage of sufentanil and the respective reactions to endotracheal intubation was presented in Fig. 3.

55.88% out of 34 patients showed hemodynamic index change < 20% of baseline during endotracheal intubation. 15 patients (44.12%) showed hemodynamic index change > 20% of baseline during endotracheal intubation. None of the patient showed laryngospasm, local anesthetic allergy, sore throat, or hoarseness. The amplitude of hemodynamic indexes (HR and BP) variation for each patient were shown in Fig. 4.

## Discussion

Evidences show the therapeutic uses of nebulized lidocaine in the treatment of intractable cough, asthma and reactive airway dysfunction syndrome [11–13]. In murine model of asthma, it has been investigated that nebulized lidocaine prevents airway inflammation, peribronchial fibrosis, and mucus production, and impaired airway hyperreactivity, possibly by inhibiting allergen-evoked GATA-3 expression and the subsequent up-regulation of proinflammatory cytokines and chemokines [14]. Koirala S reported a case by topical anesthesia of the vocal cords by nebulized lignocaine inhalation to facilitate fiberoptic nasotracheal intubation in a head-size parotid tumor patient, emphasizing the possibility of fiberoptic intubation in a sedated yet spontaneously breathing patient by allowing inhalation of nebulized lidocaine during fiberoptic intubation [15]. And then, nebulized lidocaine combined with fentanyl as a premedication to general anesthesia was a recommended implementation in spontaneously breathing pediatric patients undergoing rigid bronchoscopy [16].

Aerosol inhalation of nebulized local anesthesia causes fewer trauma to the oropharyngeal and laryngeal tissues and avoids the risk of inadvertent injection into a blood vessel as compared to nerve blocks, but requiring a larger dose possibly decreasing the risk of systemic toxicity [17]. Lidocaine plasma concentrations below 6.0 µg/ml are considered safe. And the average dose associated with the occurrence of neurological symptoms in healthy volunteers was about 8 mg/kg, corresponding to a plasma value of about 15 µg/ml [18]. The lidocaine plasma concentration was  $0.7 \pm 0.3$  µg/ml when inhalation of lidocaine was 5 mg/kg [19]. In our study, the time of atomization inhalation lasted 5 min, and the dose of lidocaine was about 300 mg, it was safe as lidocaine plasma concentrations was far below 6.0 µg/ml.

In our study, we used carbonated lidocaine for inhalation. The reason is that surface anesthetic effect of carbonated lidocaine is 4 times more effective than lidocaine hydrochloride [20]. Because the carbon dioxide released following permeation may produce local vasodilatation which increase the rate of absorption. In addition, as the carbon dioxide releases from the site of permeation, there is a resultant increase in pH, which augments formation of free base. The form of the local anesthetic which readily diffuses across biological membranes and facilitates the neural and vascular uptake [21].

By Adamus M, excellent intubation conditions were observed in 28%, 41% and 54%, while poor conditions were present in 31%, 7% and 3% of patients each receiving sufentanil 0.2, 0.3 or 0.4 µg/kg respectively. Therefore, sufentanil (0.3–0.4 µg/kg in combination with propofol (2 mg/kg) provided clinically acceptable intubating conditions in 93–97% patients [22]. In our study, inhalation aerosol lidocaine was accomplished prior to induction of anesthesia. The intravenous of anesthesia was achieved with propofol, rocuronium 0.9 mg/kg, and combined with adjusting different dose of sufentanil according to the reaction for intubation starting at 0.5 µg/kg. However, it was indicated that inhalation aerosol lidocaine reduced the amount of sufentanil needed for endotracheal intubation, and the EC<sub>50</sub> sufentanil with aerosol lidocaine for endotracheal intubation was only found to be 0.232 µg/kg. Twenty-three (55.88%) out of the all 34 patients showed hemodynamic index change < 20% of baseline during endotracheal intubation. It signified that combined with inhalation aerosol lidocaine for endotracheal

intubation reduced the dosage of opioids, enhanced hemodynamic stability, and provided better intubation conditions.

For the effect on regional deposition, the significant of particle aerodynamic diameter and inhalation maneuver need to be concerned [23]. Large particles (5–15  $\mu\text{m}$ ) are mainly deposited in the upper airways and trachea, intermediate-sized particles (3–5  $\mu\text{m}$ ) has tendency to be deposited in the bronchi and bronchioles, and small particles ( $\leq 3 \mu\text{m}$ ) are flowed into the alveoli [24]. The aerosol characteristics are closely related to the device of atomizer, which depends on the design of pressure swirl, airblast and ultrasonic atomizers [25]. The ultrasonic atomizers operate at different frequencies, which are well with the median droplet size [26]. The piezoelectric part of the ultrasonic atomizer (YUWELL 402B) produced 35% carbonated lidocaine particle sizes above 5.0  $\mu\text{m}$ , which providing good surface analgesic effect in upper airway and trachea. The maximum rate of aerosol inhalation was more than 3.0 ml/min. And it just took 10 min to prepare and finish the whole process of inhalation.

A major limitation of this study is that each patient routinely received lidocaine for a fixed period of time (5 min) with aerosol inhalation, not according to the patient's individual differences, which might impact the results. Moreover, only 35% of the particle of aerosol inhalation is the ideal size for the upper airways. A more efficient method or medical facilities of aerosol inhalation for surface anesthesia of upper airway is still worthy of further exploration.

The advantages in lidocaine inhalation for airway anesthesia by ultrasonic atomizer are revealed in our study. Inhalation of aerosol carbonated lidocaine is expected to reduce the amount of sufentanil obviously, and then provided stable hemodynamic change which avoiding or reducing the usage of cardiovascular drugs. Therefore, for the patients who are with cardiovascular and cerebrovascular diseases, this clinical application is more suitable that add the key step about aerosol inhalation of lidocaine before endotracheal intubation in anesthesia induction.

## Abbreviations

ABP: Arterial blood pressure; ASA: American Society of Anesthesiology; BP: Blood pressure; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; EC50: Concentration for 50% of maximal effect; ECG: Electrocardiogram; P: Pulse; SpO<sub>2</sub>: Pulse oxygen saturation; TCI: Target control infusion; TOF: Train of four

## Declarations

### Acknowledgements

Not applicable.

### Authors' contributions

QQX and ZQZ were the co-first authors of this article, responsible for the experiment and data analysis. LA was responsible for the patient data collection. JQL took part in revising this article, and gave constructive advices to this study. XBT, the corresponding authors of this article in charge of the project, was responsible for the expenses, and were involved in the design of the project and modified the manuscript. All authors read and approved the final manuscript.

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## **Availability of data and materials**

The data of this article is available from the corresponding author. The email address of the corresponding author is tianxb@hust.edu.cn.

## **Ethics approval and consent to participate**

The study was conducted accordance to the principles of Declaration of Helsinki. After obtaining institute ethical committee approval (referral number S308, dated Nov 22, 2017) at Tongji hospital, Tongji Medical College, Huazhong Science and Technology University, the study was registered prospectively with Chinese Registry of Central Trial (ChiCTR-IOR-17014198) before the beginning of patient enrolment, and we have obtained the informed consent which was written of all participants in the study.

## **Consent for publication**

There is no personal information in this article, so it is not applicable.

## **Competing interests**

The authors declare that they have no competing interests.

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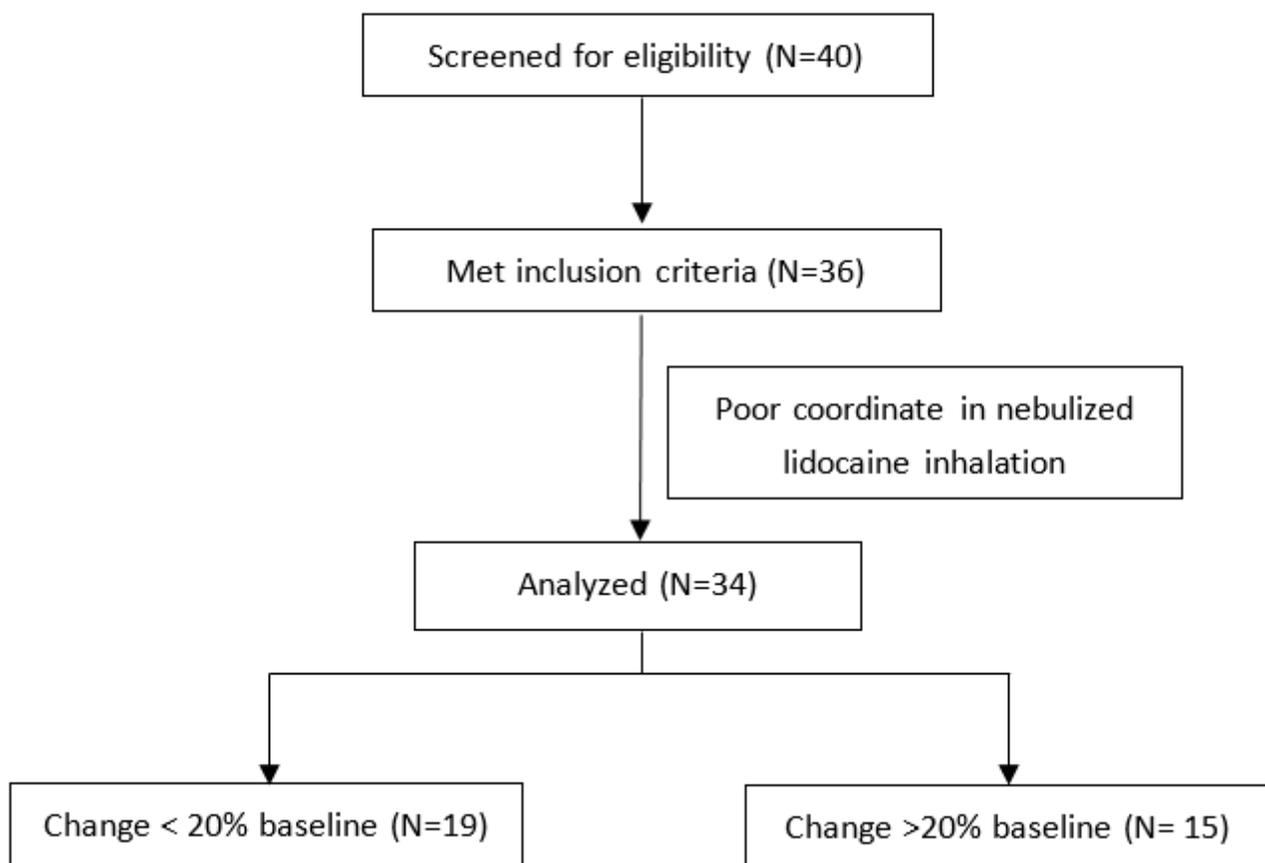
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## Figures



**Figure 1**

Study flow diagram

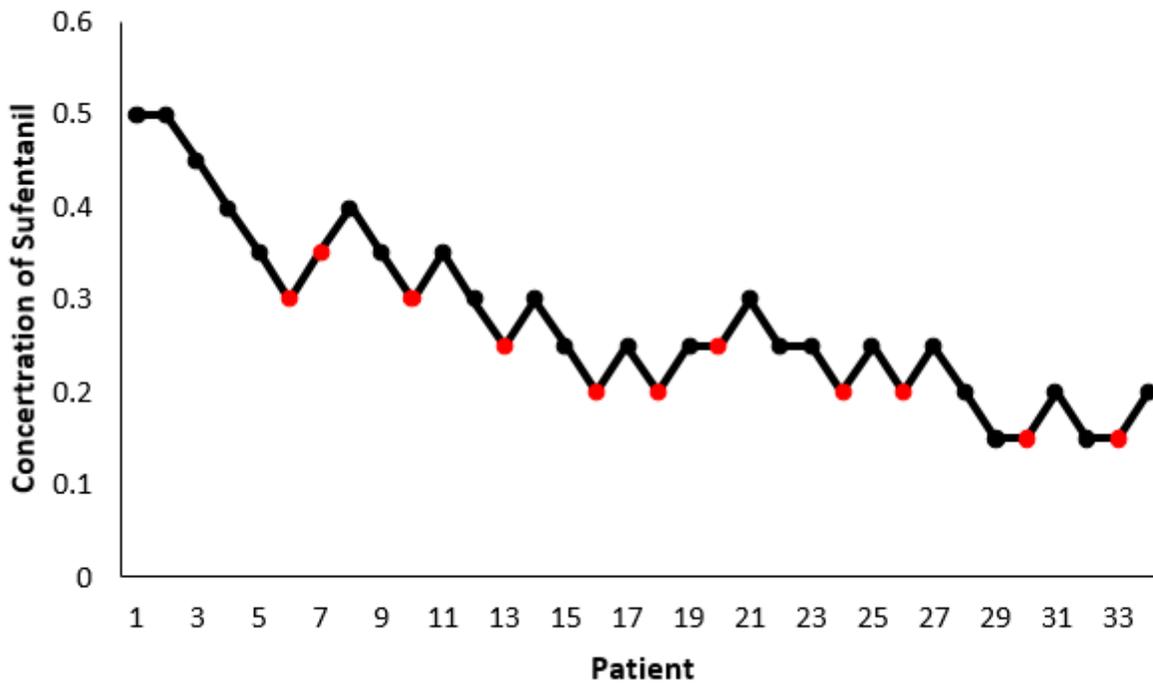


Figure 2

The 34 consecutive patients were attempted, and the concentration of sufentanil was determined according to the Dixon and Massey's up-and-down method.

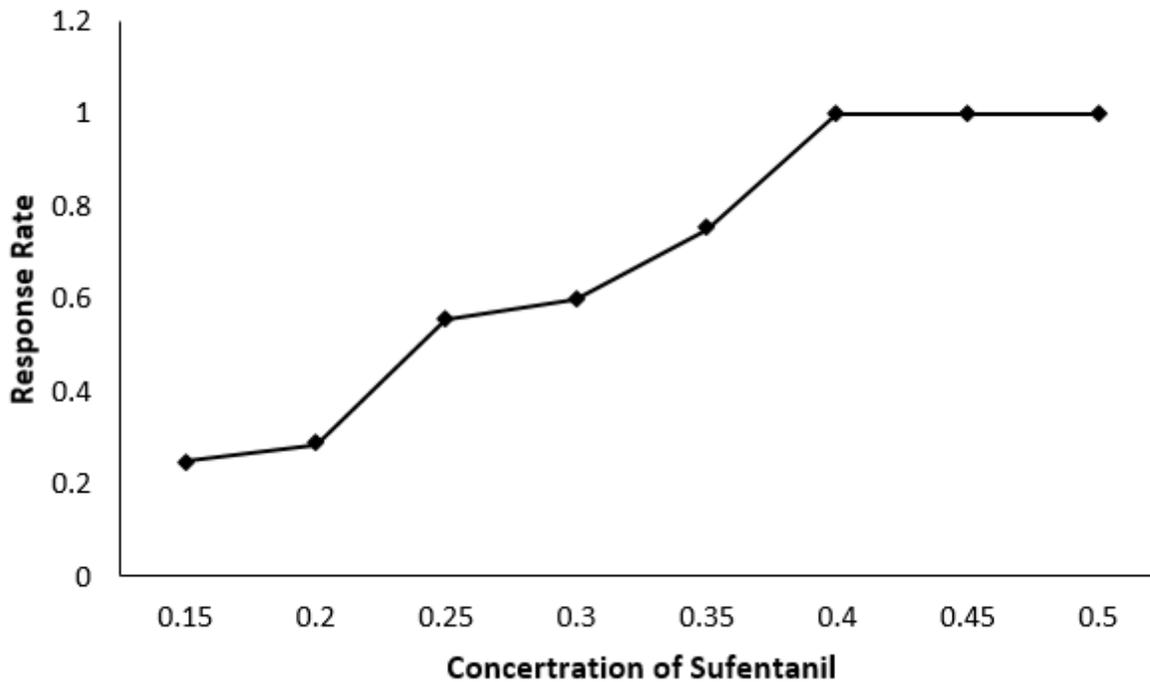


Figure 3

Concentration response curve of sufentanil and the respective reactions to endotracheal intubation was plotted from probit analysis.

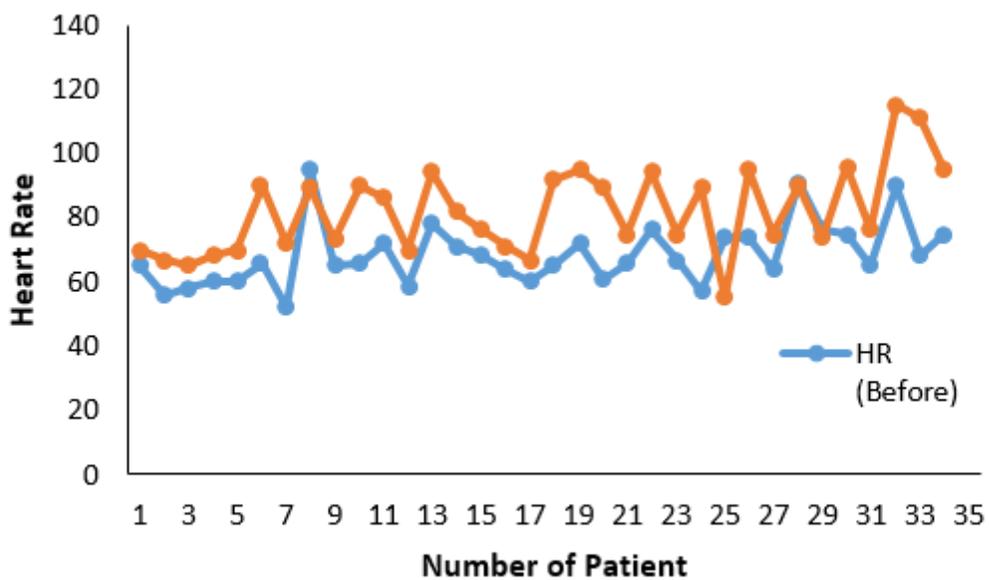


Figure 4

The heart rate values of 34 patients before and after endotracheal intubation were shown.