

## The Utility of Remifentanil Compared with Nitroglycerin for Deliberate Hypotensive Anaesthesia throughout Tympanoplasty. Randomized and Observer-Blinded Clinical Trial

Nagat S. EL-Shmaa<sup>1\*</sup>, Ashraf E Alzeftawy<sup>1</sup> and Ahmed Younes<sup>2</sup>

<sup>1</sup>Department of Anesthesia and Surgical ICU, Faculty of Medicine, Tanta University, Egypt

<sup>2</sup>Department of Ear, Nose and Throat, Faculty of Medicine, Tanta University, Egypt

\*Corresponding author: Nagat S. EL-Shmaa, Department of Anesthesia and Surgical ICU, Faculty of Medicine Tanta University, Egypt, Tel: +0020 1211865637; E-mail: nagat\_elshmaa@yahoo.com

Received date: November 21, 2017; Accepted date: November 28, 2017; Published date: December 13, 2017

Copyright: © El-shmaa NS, et al. 2017. This is an open-access article distributed under the terms of the creative commons attribution license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

**Background:** The purpose of this randomized observer-blinded clinical trial was to evaluate the utility of remifentanil compared with nitroglycerin for deliberate hypotensive anaesthesia throughout tympanoplasty.

**Methods:** Patients planned for elective tympanoplasty under general anaesthesia were allocated to receive either intravenous infusion of nitroglycerin 2-5 µg/kg/min (group NTG), or remifentanil 0.2-0.5 µg /kg/min (group REMI). The primary outcome measures were to keep up MAP between 60 and 70 mmHg with ideal vision of operative site.

**Results:** Both studied agents induced deliberate hypotensive anaesthesia and achieved ideal vision of the surgical site by decreasing bleeding, but optimum vision was provided at reasonable hypotension (MAP 70-75) in group REMI however similar situation was provided at MAP 65–69 mmHg in group NTG.

**Conclusion:** Remifentanil and nitroglycerin are safe, efficient and might be advisable for deliberate hypotensive anaesthesia throughout tympanoplasty. However, remifentanil was superior as it provided optimum vision of the surgical site through decreasing intra operative bleeding with reasonable reduction in MAP, and mild tachycardia throughout tympanoplasty.

**Keywords** Deliberate hypotension; Tympanoplasty; Nitroglycerin; Remifentanil

### Introduction

Middle ear Haemostasis is considered special issue for the anesthetist because even minimal bleeding diminishes vision in surgical site, prolongs the surgical time and increases the complications [1]. Deliberate hypotension can be accomplished by diminishing blood pressure at a lower level (40-50%) of its basal value or intentionally and reversibly diminishing mean arterial blood pressure (MAP) to 60 mmHg and maintaining it during surgery [2]. There was a variety of methods and drugs that can be used for deliberate hypotensive anaesthesia such as calcium antagonists, vasodilators, beta blockers, or by using anesthetic agents like inhalational drugs, opioids and propofol [3-7]. Adverse side effects associated with these medications include the possibility of cardiac arrhythmia and myocardial depression, vasodilators resistance, potential cyanide toxicity as with sodium nitroprusside and delayed recovery. Perfusion of the vital organs is considered a special adverse effect of deliberate hypotensive anaesthesia, additionally; effective hypotensive medications have concentration-dependent adverse effects which can be decreased by additive agents [6]. Perfect hypotensive drugs have to be easy to use and prescription with a short onset and offset time without toxic metabolites, have little or no side effects on vital organs, and have expecting and dose-dependent adverse effects [8].

Remifentanil is powerful and highly selective opioid with ultra-short acting µ- receptor agonist which has short onset time of about 1 min, rapidly provides a stable condition, rapidly metabolized by blood and tissue nonspecific esterases enzymes with short elimination half-life less than 10 min that is independent of dose, time of infusion, renal or hepatic function. Additionally, it has moderate anti-hypertensive action without reflex tachycardia or rebound hypertension [9].

Nitroglycerin (NTG) is directly acting as a vasodilator agent and provides deliberated hypotensive anaesthesia since it has a rapid onset time, be easily titrated and short time of elimination. But, it leads to increase heart rate (HR) and congestion at the operative field leading to increase bleeding [10].

As no comparative study was performed between remifentanil and nitroglycerin infusion to provide deliberate hypotensive anaesthesia during tympanoplasty, the purpose of the current clinical trial was to evaluate the safety and efficacy of remifentanil compared with nitroglycerin for deliberate hypotensive anaesthesia throughout tympanoplasty.

### Materials and Methods

Institutional Ethical Committee approval and written informed consent were signed and obtained for our randomized, double-blinded clinical trial. During the period from April 2016 to April 2017; 60 patients of both genders aged 18 to 60 years with an American Society of Anesthesiologists physical status 1 to 2 who were prepared for

tympanoplasty under general anesthesia were enrolled, following the CONSORT 2010 statement in achieving our clinical trial.

Exclusive criteria were; patients aged  $\leq 18$  years, hypersensitivity to the studied drugs, neuropsychiatric disorders, current opioid or substance abuse, kidney, heart, liver diseases, coagulopathy or drugs affecting coagulation.

The clinical trial "blind" group consists of: the working ENT surgeon, nurses and clinical trial participants. Anesthetists carried out the general anaesthesia (GA) were not unaware to studied medications used and they were not one of the clinical trial personals. However, anesthetists who collecting, analysing the data and preserving files of various measurements were blinded of patient grouping or agents used and were included in the clinical trial personals. Therefore, blinding of our clinical trial was actually provided.

By utilizing a computer-generated series of random numbers and sealed envelopes, all patients were allocated to two groups (30 patients in each group) depending on the studied agent given; nitroglycerin group (group NTG) or remifentanil group (group REMI). Each envelope was opened before induction of anesthesia.

Group NTG: received intravenous nitroglycerin infusion 2–5  $\mu\text{g}/\text{kg}/\text{min}$ .

Group REMI: received intravenous remifentanil infusion 0.2–0.5  $\mu\text{g}/\text{kg}/\text{min}$ .

In each group MAP was reduced gradually until the working surgeon informed target average category scale (ACS=2-3), [11] or until optimum MAP (60mmHg) was achieved. In every patient if MAP and heart rate (HR) maintained not changed throughout deliberate hypotension or kept for 5–10 min at its value, working surgeon assessed quality of the surgical site by ACS then the anesthetist approved his evaluation.

#### Average category scale (ACS)

- 1) No bleeding,
- 2) Slight bleeding-no suctioning of blood required,
- 3) Slight bleeding-occasional suctioning required. Surgical field not threatened,
- 4) Slight bleeding-frequent suctioning required. Bleeding threatens surgical field a few seconds: after suction is removed,
- 5) Moderate bleeding-frequent suctioning required. Bleeding threatens surgical field directly after suction is removed,
- 6) Severe bleeding-constant suctioning required. Bleeding appears faster that can be removed by suction. Surgical field severely threatened and surgery not possible) [11].

Every patient was nothing per oral (NPO) for 8 h as per the standard and following arriving the patients at the operating theatre the patients were monitored continuously by non-invasive arterial blood pressure, pulse oximetry and electrocardiography. Baseline MAP, HR and oxygen saturation were collected and recorded. Lactated ringer's solution 5 ml/kg was given after securing IV line. Ceftriaxone 1 g IV was given within an hour before surgery as antibiotic prophylaxis. Every patient was premedicated by midazolam 0.02 mg/kg IV in the holding area. Induction of GA was carried out by using IV fentanyl 1.5  $\mu\text{g}/\text{kg}$ , propofol 1.5 mg/kg, and for tracheal intubation rocuronium 0.6 mg/kg was used, then maintenance dose of rocuronium was 0.15b

mg/kg. Maintenance of GA was achieved by isoflurane 1.0 MAC in oxygen and the end-tidal carbon dioxide concentration (EtCO<sub>2</sub>) was preserved at a range of 30–40 mmHg. Before operation commenced, for further decrease of the amount of surgical site bleeding; patient head was elevated up about 20° then 10 ml lignocaine- epinephrine (1: 200,000) was administered at skin behind the ear by the same working surgeon in every patient. After induction of GA; HR, Systolic, diastolic, and MAP were collected and recorded every 3 min for 15 min and then every 5 min until the end of operation. Bradycardia was considered when HR < 50 beats/min and managed with atropine 0.01 mg/kg IV. Hypotension was considered when MAP < 60 mm Hg and was treated with Ephedrine 5 mg IV initially then by 50% decrease in the dose of infusion and finally stop the infusion if no improvement. The vision of the surgical site was assessed by the same working surgeon depending on the ACS [11]. The studied agents were stopped about five minutes before finishing the operation. Neuromuscular blocker's reversal was given (neostigmine 0.05 mg/kg plus atropine 0.02 mg/kg mixture IV) and tracheal tube was removed if respiration was regular and tidal volume was appropriate in a fully conscious patient. Measures of MAP were recorded and analysed in three subgroups of 5 mm Hg; consequently 3 subgroups were carried out in the two groups; MAP 70-75, 65–69 and 60–64 mmHg. Surgery time, anesthesia time, deliberate hypotensive anaesthesia times were analysed. Adverse effects were reported. A four-point scale was used for surgeon's satisfaction by the same working surgeon (1=bad, 2=moderate, 3=good, 4=excellent) [12].

#### Statistical Analysis

SPSS version 17 (SPSS Inc., Chicago, IL, USA) was utilized for statistical analysis. Adjustment of sample size was performed before enrolment of the patient. depending on former studies [1, 3]; to achieve an acceptable power of about 80% and an alpha error of about 0.05 to achieve 10 mm Hg statistically significant difference in MAP, and to provide 20% difference between-groups in the ACS that used to assess vision in the operative site. It is essential to enrol 30 patients in each group to avoid a possibility of patient's dropouts. The sample size calculation was performed using EpI-Info 2002 software statistical package designed by World Health Organization (WHO) and by Centres for Disease Control and Prevention (CDC). Measures were reported in mean and standard deviations and utilizing Student's-t-test and Chi-square test for analysis. P value <0.05 was considered significant.

#### Results

Seventy-two patients were evaluated for eligibility, sixty patients were enrolled in the clinical trial and the outcomes measures of 60 patients were analysed (Figure 1). Demographic properties were comparable in both groups (Table 1).

In (Table 2) time (min) to achieve optimum ACS of 2–3 was statistically significant shorter in group REMI than group NTG ( $3.5 \pm 2.1\text{min}$  VS.  $5.2 \pm 2.5$ ,  $P=0.01$ ) while anesthesia time (min), surgical time (min) and deliberate hypotensive anaesthesia time (min) were comparable in both groups ( $p>0.05$ ) but surgeon's satisfaction was statistically significant difference in group REMI than group NTG ( $p=0.01$ ). In (Table 3) Systolic, diastolic and MAP were not statistically significant differences in studied groups based on MAP when compared in three different subgroups ( $p=0.43$ ). While, HR maintained statistically significant lower in group REMI than group NTG ( $p=0.01$ ). Group REMI achieved ideal vision in surgical field

(ACS  $2.5 \pm 0.5$ ) earlier at MAP 70–75 mmHg than group NTG (ACS  $3.5 \pm 0.5$ ) demonstrating that we needed more hypotension to provide ideal vision in operative field in group NTG. ACS  $2.4 \pm 0.3$  was achieved at MAP 60–65 mm Hg in group NTG. In this clinical trial ACS in group REMI was superior to that in group NTG at each MAP level ( $P=0.02$ ) demonstrating that remifentanil achieved optimal vision of operative site compared with group NTG. There were no statistically significant differences in adverse actions of deliberate hypotensive anaesthesia in both groups.

Figure 1 demonstrates the flowchart for the current investigation, in which 72 patients were evaluated for eligibility and 60 adult patients were included in the clinical trial. The results of 60 patients were analysed.

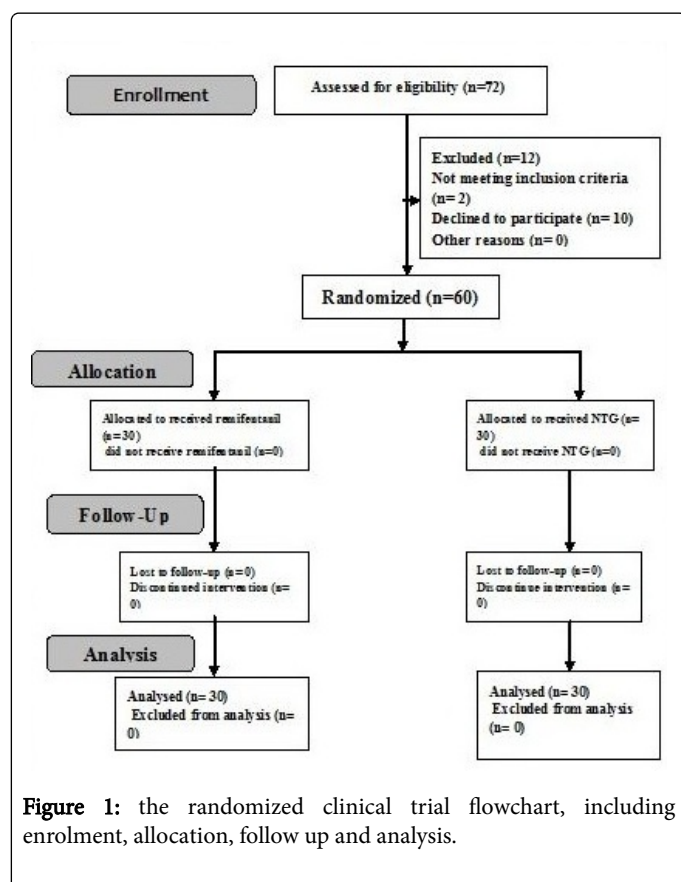


Figure 1: the randomized clinical trial flowchart, including enrolment, allocation, follow up and analysis.

Table 1 demonstrating that no significant differences were noted between the studied groups for demographic properties of the subjects ( $P>0.05$ ).

Variables	Group NTG(n=30)	Group REMI(n=30)	P value
Age (years)	37.6 ± 8.3	39.3 ± 6.5	0.4
gender (M: F)	13:17	12:18	0.8
Weight (Kg)	74.7 ± 7.8	80.5 ± 9.2	0.3
ASA (I:II)	17:13	16:14	0.6

Table 1: Comparison of demographic patients' characteristics between the studied groups (Mean ± SD).

Variables	Group NTG (n=30)	Group REMI (n=30)	P value
The time to achieve target ACS (min)	5.2 ± 2.5	3.5 ± 2.1*	0.01
surgical time (min)	135.75 ± 28.4	127.48 ± 25.8	0.090
anaesthesia time (min)	146 ± 26.3	138 ± 25.7	0.13
deliberate hypotension anaesthesia time (min)	139 ± 24.5	132 ± 23.2	0.33
Surgeon's satisfaction (1-4)	2.8 ± 0.7	3.2 ± 0.6*	0.0008 (<0.01)

\* Denotes statistically significant  $p < 0.05$ .

Table 2: Comparison of operative variables between the studied groups (Mean ± SD).

## Discussion

Deliberate hypotensive anaesthesia is a famous technique for its capacity to control blood loss, provide optimum vision of surgical site diminishes surgical manipulations in addition to decrease the occurrence of serious adverse effects and diminishes duration of operation. Nonetheless, its prolonged application may lead to cardiovascular instability, cerebrovascular insufficiency and hypoxia [13]. The basic concept for deliberate hypotensive anaesthesia is intentionally and reversibly reduction of arterial blood pressure to the values that blood loss is negligible; but the vital organs perfusion is appropriately kept up [14]. There were Limited information in the studies about the utilization of IV infusion of remifentanil compared with nitroglycerin for providing deliberate hypotensive anaesthesia throughout tympanoplasty.

The significant results of the current investigation are; both nitroglycerin and remifentanil accomplished deliberate hypotensive anaesthesia as required for tympanoplasty and MAP was kept in comparable range in studied groups throughout the period of deliberate hypotensive anaesthesia. Nevertheless, ideal vision in the operative site with ideal ACS 2–3 was provided with minimal reduction of MAP in remifentanil group but comparable situations were provided with moderate decrease of MAP in nitroglycerin group. In concurrence with the present outcomes; Zet al. [15]; compared between nitroglycerin and remifentanil utilization in deliberate hypotensive anaesthesia throughout intracranial aneurysm surgery and concluded that remifentanil- incited deliberate hypotension was superior to nitroglycerin- incited deliberate hypotension and had many clinical benefits for blood preservation.

Ryu et al. [16]; demonstrated the clinical effectiveness of remifentanil versus magnesium sulphate throughout operation of middle ear and reported that remifentanil and magnesium sulphate when used in combination with sevoflurane gave sufficient deliberate hypotensive anaesthesia and ideal vision of the operative site during operation. Also, Celebiet al. [17]; assessed the efficiency of remifentanil and, esmolol as additional agents for deliberate hypotensive anaesthesia on operative situation during tympanoplasty surgery and found that both remifentanil and esmolol provided satisfactory deliberate hypotension and comparative surgical conditions.

Different clinical medications have been used for deliberate hypotensive anaesthesia. Nonetheless, drug adverse effects should not

be ignored, such as myocardial depression, arrhythmia, potential cyanide poisoning, prolonged recovery, etc. in the present investigation; we conducted deliberate hypotensive anaesthesia with remifentanil versus nitroglycerin. Induction of deliberate hypotensive anaesthesia leads to the release of endogenous catecholamines. Remifentanil is a powerful, ultra-short acting  $\mu$ -opioid receptor agonist and has moderate advantage of anti-hypertension. The possible anti-hypertensive mechanisms of actions of remifentanil are as followings [18,19]: [1] Central nervous or autonomic system inhibition. [2] Catecholamine discharge suppression during surgery, particularly on adrenaline. [3] Dilation on blood vessels through endothelial-

dependent release of nitric oxide and prostacyclin (NO); [4] Dilation on blood vessels through voltage-dependent calcium channel (endothelial-independent). Nitroglycerin becomes vasodilator by discharging NO, which leads to reflex tachycardia. But it might also be harm when it is utilized for long time, as it could easily lead to vascular tolerance, cyanide poisoning and rebound hypertension. Tachycardia is a dangerous damage to the cardiovascular system, as it could increase myocardial oxygen consumption and diminish oxygen supply [20]. Consistent with this, our results showed that HR kept statistically significantly lower in group REMI than group NTG.

MABP subgroup (mmHg)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Mean arterial blood pressure (mmHg)	Heart rate/min	ACS
Group NTG					
Base line	117 ± 18	65 ± 5	78 ± 14	96 ± 11	
75-70	99 ± 5	59 ± 2	66 ± 4	88 ± 10	3.4 ± 0.4
69-65	90 ± 6	51 ± 3	65 ± 3	84 ± 7	2.8 ± 0.4
64-60	81 ± 7	48 ± 2	61 ± 5	80 ± 6	2.4 ± 0.3
Group REMI					
Base line	119 ± 17	66 ± 4	80 ± 18	95 ± 12	
75-70	95 ± 7	63 ± 3	68 ± 5	81 ± 7*	2.5 ± 0.5*
69-65	87 ± 6	50 ± 4	67 ± 6	78 ± 3*	2.3 ± 0.4*
64-60	79 ± 8	48 ± 3	63 ± 4	67 ± 8*	2.1 ± 0.3*
Data are mean ± SD.					
Denotes statistically significant P<0.05.					

**Table 3:** Comparison of hemodynamic and (ACS) variables between the studied groups (Mean ± SD).

Herein, the surgery time was slightly shorter in group REMI than group NTG. The surgery time has been found to be shorter when deliberate hypotensive anesthesia was well established since optimum vision of operative site and decrease time wasting in frequent suction [21].

Degoute et al. [1]; used a combination of remifentanil and propofol infusion after a bolus dose of remifentanil in tympanoplasty; they assessed middle ear blood flow by laser-Doppler flow meter and demonstrated a statistically significant reduction, subsequently an ideal operative field. In contrast to our investigation, we did not start with a bolus dose of remifentanil and surgical field evaluation was done by ACS not by objective method, like with that of Degoute et al.

Limitations of this investigation included; first, we did not use objective technique for assessment of deliberate hypotension as catecholamine or stress hormone levels. Second, transoesophageal echocardiography, cardiac output, invasive MAP and laser-Doppler flow meter monitoring for measurement of blood flow in the middle ear could give an accurate idea about various factors assuming bleeding and deliberated hypotensive anaesthesia.

## Conclusion

Remifentanil and nitroglycerin are safe, efficient and might be advisable for deliberate hypotensive anaesthesia throughout tympanoplasty. However, remifentanil was superior as it provided optimum vision of the surgical site through decreasing intra operative bleeding with reasonable reduction in MAP, and mild tachycardia throughout tympanoplasty.

## Acknowledgements

We (the authors) would like to thank the members at the Operation Theatre of Tanta University Hospital, Tanta; for their assistance in completing this study.

## References

1. Degoute CS, Ray MJ, Manchon M (2001) Remifentanil and controlled hypotension; comparison with nitroprusside or esmolol during tympanoplasty. *Can J Anaesth* 48: 20-27.
2. Van Aken H, Miller D (2000) Deliberated hypotension. In: Miller RD, editor. *Anesthesia*. Churchill Livingstone Inc, New York, USA.
3. Sajedi P, Rahimian A, Khalili G (2016) Comparative evaluation between two methods of induced hypotension with infusion of remifentanil and labetalol during sinus endoscopy. *J Res Pharm Pract* 5: 264-271.

4. Ankichetty SP, Ponniah M, Cherian VT, Thomas S, Kumar K (2011) Comparison of total intravenous anaesthesia using propofol and inhalational anaesthesia using isoflurane for controlled hypotension in functional endoscopic sinus surgery. *J Anaesthesiol Clin Pharmacol* 77: 328-332.
5. Tirelli G, Bigarini S, Russolo M, Lucangelo U, Gullo A (2004) Total intravenous anaesthesia in endoscopic sinus surgery. *Acta Otorhinolaryngol Ital* 24: 137-144.
6. Degoute CS (2007) Controlled hypotension: a guide to drug choice. *Drugs* 67: 1053-1076.
7. Rodrigo C (1995) Induced hypotension during anesthesia with special reference to orthognathic surgery. *Anesth Prog* 42: 41-58.
8. Blowey DL (2001) Antihypertensive agents: Mechanisms of action, safety profiles, and current uses in children. *Curr Ther Res Clin Exp* 62: 298-313.
9. Kapila A, Glass PS, Jacobs JR, Muir KT, Hermann DJ (1995) Measured context-sensitive half-times of remifentanil and alfentanil. *Anesthesiology* 83: 968-975.
10. Srivastava U, Dupargude AB, Kumar D, Joshi K, Gupta A (2013) Controlled Hypotension for Functional Endoscopic Sinus Surgery: Comparison of Esmolol and Nitroglycerine. *Indian J Otolaryngol Head Neck Surg* 65: 440-444.
11. Fromme GA, MacKenzie RA, Gould AB, Lund BA, Offord KP (1986) Controlled hypotension for orthognathic surgery. *Anesth Analg* 65: 683-686.
12. Das A, Mukherjee A, Chhale S, Chattopadhyay S, Halder PS (2016) Induced hypotension in ambulatory functional endoscopic sinus surgery: A comparison between dexmedetomidine and clonidine as premedication. A prospective, double-blind, and randomized study. *Saudi J Anaesth* 10: 71-77.
13. Turan G, Dincer E, Ozgultekin A, Uslu C, Ormanci F (2007) Comparison of Dexmedetomidine, Remifentanil and Esmolol In Controlled Hypotensive Anaesthesia. *The Internet Journal of Anesthesiology* 17: 1-7.
14. Tobias JD (2002) Controlled hypotension in children: A critical review of available agents. *Paediatr Drugs* 4: 439-453.
15. Xuekang Z, Qian H, Zhiyi L, Haijin H, Qin Z (2015) Comparison between nitroglycerin and remifentanil in acute hypervolemic hemodilution combined with controlled hypotension during intracranial aneurysm surgery. *Int J Clin Exp Med* 8: 53-59.
16. Ryu JH, Sohn IS, Do SH (2009) Controlled hypotension for middle ear surgery: a comparison between remifentanil and magnesium sulphate. *Br J Anaesth.* 103: 490-495.
17. Celebi N, Artukoglu F, Dal D, Saricaoglu F, Celiker V (2007) Effect of hypotensive anesthesia on cognitive functions. A comparison of esmolol and remifentanil during tympanoplasty. *Saudi Med J* 28: 1357-1361.
18. Schuttler J, Albrecht S, Breivik H (1997) A comparison of remifentanil and alfentanil in patients undergoing major abdominal surgery. *Anaesthesia* 52: 307-317.
19. Sebel PS, Hoke JF, Westmoreland C (1995) Histamine concentrations and hemodynamic responses after remifentanil. *Anesth Analg* 80: 990-993.
20. Tao DQ, Yang ZM, Lu LS (2007) The observation of Remifentanil-induction controlling hypotension for intracranial aneurysm clipping. *Mod Med J Chin* 9: 74-76.
21. Jacobi KE, Bohm BE, Richauar AJ, Jacobi C, Hemmerling TM (2000) Moderate controlled hypotension with sodium nitroprusside does not improve surgical condition or decrease blood loss in endoscopic sinus surgery. *J Clin Anesth* 12: 202-207.