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ORIGINAL ARTICLE

# Comparison of the hemodynamic effects of nitroprusside and remifentanil for controlled hypotension during endoscopic sinus surgery

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**Abstract**
*Purpose* Controlled hypotension (CH) is a well-established technique to decrease blood loss and improve surgical visibility. Although nitroprusside and remifentanil have been safely and effectively used for this purpose, the hemodynamic changes that occur during CH are unclear. This study compared the effects of nitroprusside and remifentanil on hemodynamics using a noninvasive cardiac output monitor (Cheetah NICOM®; Cheetah Medical Inc., Maidenhead, Berkshire, UK) for endoscopic sinus surgery (ESS).
*Methods* Twenty-eight adult patients scheduled for ESS were randomly assigned to the nitroprusside group ($n = 14$) or remifentanil group ($n = 14$). After anesthesia induction, hypotension was induced with continuous infusion of nitroprusside or remifentanil at a target mean arterial blood pressure (MAP) of 60–70 mmHg. Cardiac index (CI), stroke volume index (SVI) and total peripheral resistance index (TPRI) were measured at 10-min intervals.
*Results* The heart rate was higher and SVI was lower in the nitroprusside group than in the remifentanil group during CH. There were no significant differences in MAP, CI or TPRI between the two groups. Both nitroprusside and remifentanil reduced MAP and TPRI during CH compared with baseline values. However, there was no significant change in CI.
*Conclusions* Both nitroprusside and remifentanil were effective to induce CH and maintain CI during CH.

**Keywords** Cardiac output · Hemodynamics · Hypotension, controlled · Nitroprusside · Remifentanil

## Introduction

Controlled hypotension (CH) means deliberately reducing systolic blood pressure down to 80–90 mmHg or reducing mean arterial blood pressure (MAP) to 50–70 mmHg or 30 % from the baseline MAP. It has been effectively used for various surgeries such as middle ear surgery, endoscopic sinus surgery (ESS) and orthopedic surgery, because it improves surgical visibility and reduces the need for blood transfusion by reducing bleeding [1–5].

Pharmacological agents used to induce CH include vasodilators, α-receptor and β-receptor blockers, as well as inhalation anesthetics at high concentrations and so on. Among those agents, nitroprusside has been widely used for decades [1, 3, 6]. It effectively controls blood pressure by directly inducing peripheral vasodilation with an onset time below 30 s and recovery time below 2 min [1].

Remifentanil has recently been recognized as an agent for creating a state of CH. It is a short-acting μ-opioid agonist that is characterized by its rapid onset and recovery times. When remifentanil is administered with propofol or other inhalation anesthetics, CH can be successfully induced and surgical visibility is improved without affecting the microcirculation of local tissues [2, 3]. Hypotension and bradycardia could occur when remifentanil is administered, but there is little information about

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other hemodynamic variables such as changes of cardiac output, stroke volume and total peripheral resistance.

The purpose of this study was to provide a safe management of anesthetic procedures by comparing changes of the hemodynamic variables in two groups of patients who were administered either with nitroprusside or remifentanil to induce a state of CH during general anesthesia in ESS.

## Materials and methods

This study was approved by the Institutional Review Board of Jeju National University Hospital (Ref: JEJUNUH 2012-04-003-001) and registered in protocol registration system (ClinicalTrial.gov Ref: NCT02001298). Written informed consent was obtained before enrollment.

Subjects were between 20–60 years and included those who were scheduled to undergo ESS under general anesthesia with an American Society of Anesthesiologists class of I or II. A total of 28 patients were randomly assigned to either the nitroprusside group ($n = 14$) or the remifentanil group ($n = 14$) using computer-generated codes. Patients with cardiovascular diseases such as hypertension, coronary artery disease, heart valve disease or heart failure were excluded from this study. Other exclusion criteria were allergies to the study drugs, cerebrovascular disease with crucial cerebral blood flow control, pregnancy and also other uncontrolled severe systemic diseases.

No patient received preanesthetic medications. When a patient entered the operating room, electrocardiography, pulse oxymetry and non-invasive blood pressure (BP) were monitored (SureSigns VM8®, Philips medical systems, USA). Baseline values of hemodynamic variables were measured using a noninvasive cardiac output monitor (Cheetah NICOM®; Cheetah Medical Inc., Maidenhead, Berkshire, UK). General anesthesia was induced with thiopental 4–5 mg/kg and tracheal intubation was facilitated with rocuronium 0.6 mg/kg. The anesthesia was maintained with an end-tidal concentration of sevoflurane of 1 minimum alveolar concentration at 2 L/min of $O_2$ and $N_2O$ and the lungs were ventilated to maintain an end-tidal $CO_2$ of 30–35 mmHg. The operation field was infiltrated with local anesthetic solution (2 % lidocaine with 1:100,000 epinephrine). Ringer's solution was administered continuously at a rate of 4 ml/kg/h and 3 ml/ml of lost blood.

The CH was maintained at the target mean blood pressure (MAP) of 60–70 mmHg [7]. Nitroprusside or remifentanil was initially infused at 0.5 μg/kg/min to induce the hypotension, and the rate of infusion was properly regulated to maintain the target MAP. The infusion of nitroprusside or remifentanil was discontinued when the major surgical procedure was completed. At the end of surgery, the neuromuscular blockade was reversed with neostigmine 1.5 mg and glycopyrrolate 0.4 mg. Fentanyl 1 μg/kg was administered for pain control.

In the post-anesthesia care unit, postoperative pain and any adverse effects including nausea and vomiting were evaluated using a numerical rating scale (0–10). If the numerical rating scale was more than 5 or the patient requested medication, rescue analgesic (ketorolac 30 mg) or antiemetic (ondansetron 4 mg) was administered. The post-anesthesia care unit was discharged when the modified Aldrete score was appropriate (score $\geq 9$) and the adverse symptom subsided [8].

The stroke volume index (SVI), total peripheral resistance index (TPRI) and cardiac index (CI) were measured every 10 min throughout the surgery using a NICOM.

**Table 1** Demographics, operative data and recovery profile

| | Nitroprusside group ($n = 14$) | Remifentanil group ($n = 14$) | $P$ value |
|---|---|---|---|
| Age (years) | 30.5 (22–42) | 30.5 (23.5–41) | 0.8 |
| Height (cm) | 168.5 (165.5–172.8) | 174 (170.3–176.5) | 0.1 |
| Weight (kg) | 68.5 (63.5–71.8) | 74 (64–77.5) | 0.33 |
| Gender (M/F) | 12/2 | 13/1 | 1 |
| Duration of anesthesia (min) | 147.5 (111.3–172.5) | 165 (101.3–197.5) | 0.43 |
| Systolic blood pressure before anesthesia | 128.5 (124.5–132) | 128.5 (119–136.3) | 0.13 |
| Mean blood pressure before anesthesia | 102 (96.8–103.8) | 97.5 (90.3–101.5) | 0.73 |
| Diastolic blood pressure before anesthesia | 87 (82.5–90.5) | 81 (76–86.8) | 0.09 |
| Duration of surgery (min) | 112.5 (75.5–144.0) | 136.5 (76.8–165) | 0.27 |
| Duration of controlled hypotension (min) | 75 (39.8–104.8) | 66 (50.3–126) | 0.82 |
| Total dose of nitroprusside or remifentanil (μg) | 2,475 (1,852.5–3,875) | 1,175 (1,000–1,560) | |
| Average infusion rate of nitroprusside or remifentanil (μg/kg/min) | 0.56 (0.44–0.86) | 0.24 (0.13–0.36) | |
| Rescue analgesics at PACU | 2 | 3 | 1 |
| Rescue antiemetics at PACU | 1 | 1 | 1 |
| Time to PACU discharge (min) | 42 (33–45) | 41.5 (34.3–44.5) | 0.91 |

Values are median (interquartile range) or numbers

*M* male, *F* female, *PACU* post-anesthesia care unit

These measurements were divided into four periods (before anesthesia induction, after anesthesia induction, after CH induction and after CH termination) and the mean value was obtained for each period. Baseline data were defined as measurements taken prior to anesthesia induction. Duration of CH was defined as the time from initiation to termination of the study drugs.

In an earlier study, nitroprusside increased the pulse rate by 15.35 beats/min compared with the baseline values, and the standard deviation was 14.36 in this case [9]. Assuming that remifentanil does not change the baseline pulse rate, 14 samples were needed per group at $\alpha$ error of 0.05 and $\beta$ error of 0.2.

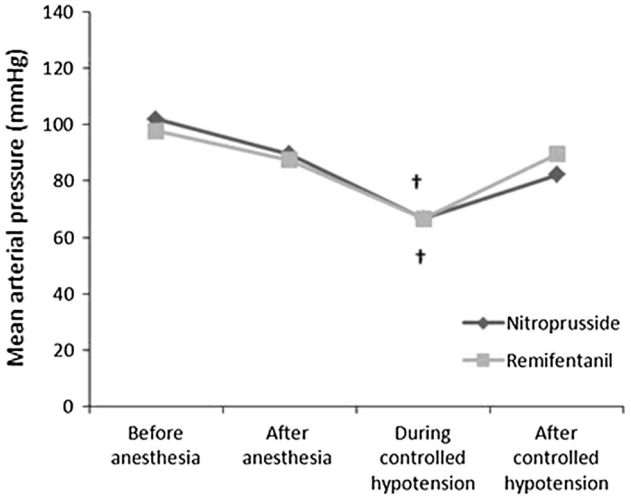


**Fig. 1** Mean arterial pressures in the groups with nitroprusside and remifentanil. Values are median values. Nitroprusside, nitroprusside infusion group; Remifentanil, remifentanil infusion group. $^{\dagger}p < 0.05$ compared with baseline value

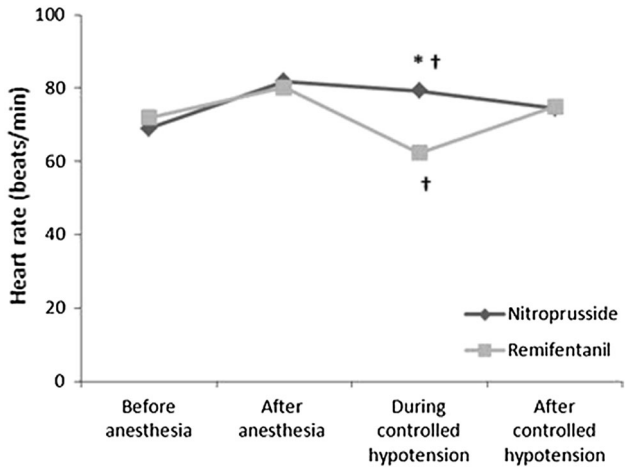


**Fig. 2** Heart rate in the groups with nitroprusside and remifentanil. Values are median values. Nitroprusside, nitroprusside infusion group; Remifentanil, remifentanil infusion group. $^{\dagger}p < 0.05$ compared with baseline value. $^{*}p < 0.05$ compared with remifentanil group

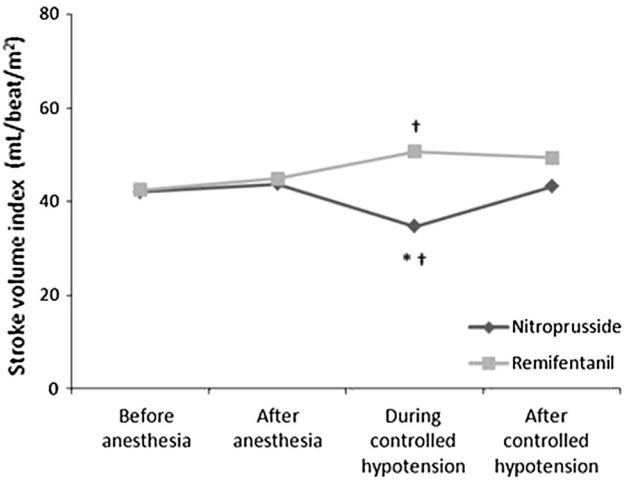


**Fig. 3** Stroke volume index in the groups with nitroprusside and remifentanil. Values are median values. Nitroprusside, nitroprusside infusion group; Remifentanil, remifentanil infusion group. $^{\dagger}p < 0.05$ compared with baseline value. $^{*}p < 0.05$ compared with remifentanil group

SPSS (IBM SPSS statistics 20 for Windows) was used for statistical analysis. The differences between groups were analyzed using the Mann–Whitney test and the categorical variables were analyzed using the Fisher's exact test. The Wilcoxon test was used to analyze the variation within groups. $p$ values <0.05 were considered statistically significant.

## Results

Patient characteristics in both groups are described in Table 1. There were no significant differences between the two groups with respect to the duration of anesthesia, surgery or CH. Recovery profile such as rescue analgesics, rescue antiemetics, and time to discharge of post-anesthesia care unit was also similar between the two groups. No patient required management for severe hemodynamic changes or reported any adverse events with regard to use of these drugs.

Baseline MAP and HR values were comparable between the groups (Figs. 1, 2). The MAP was significantly decreased in both groups during the CH period compared with the baseline value, but it was not significantly different between groups in any period (Fig. 1). The mean HR was significantly increased in the nitroprusside group during the CH period compared with baseline and was significantly different from that of the remifentanil group. The remifentanil group showed a significantly reduced HR compared with baseline values in the same periods (Fig. 2).

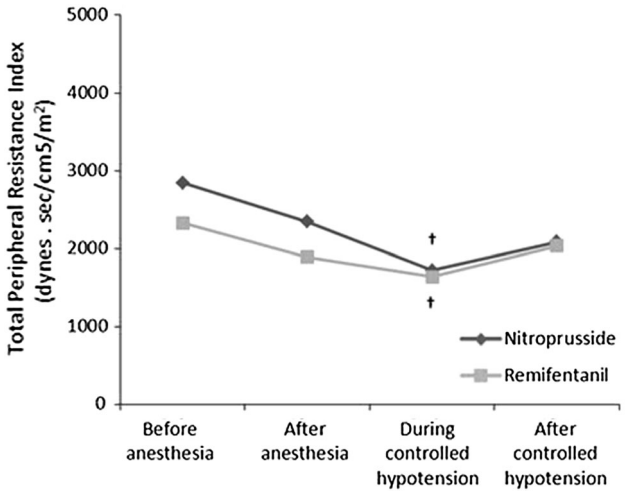


**Fig. 4** Total peripheral resistance index in the groups with nitroprusside and remifentanil. Values are median values. Nitroprusside, nitroprusside infusion group; Remifentanil, remifentanil infusion group. $^{\dagger}p < 0.05$ compared with baseline value

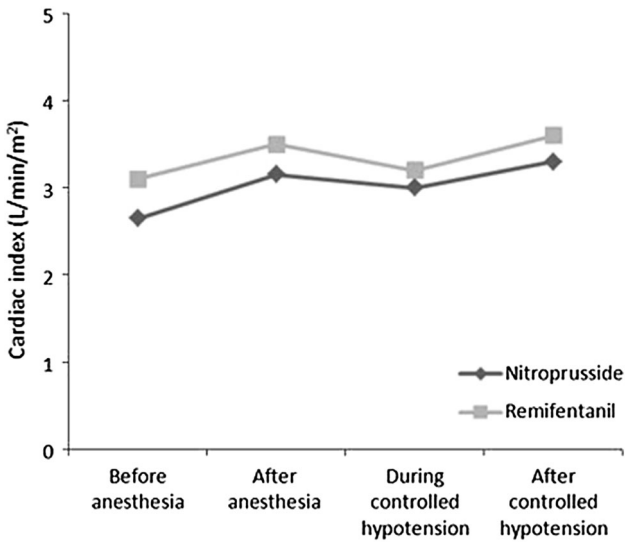


**Fig. 5** Cardiac index in the groups with nitroprusside and remifentanil. Values are median values. Nitroprusside, nitroprusside infusion group; Remifentanil, remifentanil infusion group

The SVI was significantly decreased in the nitroprusside group during the CH period compared with baseline values and was significantly different from that of the remifentanil group. The remifentanil group showed a significant increase in mean SVI compared with baseline values in the same periods (Fig. 3).

The TPRI values in both groups were significantly decreased compared with baseline values during the CH period, but did not differ significantly between groups in any period (Fig. 4). The CI did not significantly differ in any period between groups and was not decreased during the CH period (Fig. 5).

## Discussion

This study shows that both nitroprusside and remifentanil were effective to induce CH with similar hemodynamics except HR and SVI during a general anesthesia with sevoflurane. Furthermore, the CI remained without any significant change in both groups.

The ESS is performed within a narrow and limited area with high blood flow. This has led to much effort to improve surgical visibility. CH has been widely used for that purpose, as a way to control bleeding during ESS [10–12]. Nitroprusside, a potent vasodilator, has been used as a CH-inducing drug for decades. However, caution is needed in its use because it can induce undesirable changes in the cardiovascular system, such as increased myocardial contractility, reflex tachycardia and rebound hypertension, by stimulating reaction of the pressure receptor and the sympathetic nervous system [1, 13, 14]. Additionally, a previous study reported that CH using nitroprusside could cause an increase in blood flow within the mucous membrane capillaries due to vasodilation and rise of cardiac output, and therefore it could worsen surgical visibility compared with using β-blockers [9]. In this study, MAP decreased along with significant reduction of TPRI when CH was maintained using nitroprusside as it is known already. Increases in HR from the baseline value during CH were also observed, but the extent of increasing range was ≤102 beats per minute. On the other hand, cardiac output was not changed, nor were reflex tachycardia or rebound hypertension related to its termination observed. This may be attributed to the low dose of nitroprusside used in this study [15, 16].

Remifentanil is an ultra-short-acting μ-opioid receptor agonist. It appears to provoke mild to moderate hypotension and bradycardia. Although several studies have recently reported its efficacy in inducing CH and an ability to ensure a satisfactory operative field [2, 12, 17, 18], there are few reports about hemodynamic changes during CH. Kazmaier et al. [19] reported that a maintenance of anesthesia with remifentanil (0.5 μg/kg/min) and propofol reduced MAP, CI and TPRI, while the SVI was not significantly different from that in patients with coronary artery disease in an awake state. The decrease in CI was caused by reduction of HR. In our study, the maintenance with CH using remifentanil significantly decreased MAP, HR and TPRI compared with the values before anesthesia induction. However, there was no significant change in CI during CH. This gap may result from different subjects,

anesthetic agents or doses of remifentanil between the two studies.

Although the functional mechanism of nitroprusside and remifentanil is different (vasodilator vs. opioid agonist), the TPRI was significantly decreased from baseline values during CH in both groups, and the degree of reduction was not different between both groups. Remifentanil seems to have little effect on TPRI when it is used alone, but it could significantly reduce TPRI when used with other anesthetics [19]. Comparing both groups at each period, HR was higher and SVI was lower in the nitroprusside group than in the remifentanil group in the CH period, but CI was maintained without significant changes in both groups. It resulted from increased HR to compensate for decreased SVI in the nitroprusside group and increased SVI to compensate for decreased HR in the remifentanil group.

There are several limitations to this study. First, we did not evaluate surgical visibility or the satisfaction of the operating surgeon, because this study was initially designed to elucidate the changes in cardiovascular factors during CH. Therefore, the actual bleeding situation on surgical field could be different between both groups. Next, the degree of hypotension was mild. If profound hypotension is induced, the hemodynamic changes could be different from that in mild CH. Finally, we used a noninvasive cardiac output monitor to evaluate hemodynamics. The NICOM system consists of four dual electrode sensors, which are placed on the right and left side of the chest. Within each sticker, one electrode injects the high-frequency sine wave current into the body and the other electrode measures the voltage input. The pulsatile blood flows from the heart create phase shifts in alternating radiofrequency electrical currents across the patients' chest. The device calculates cardiac output using the relative phase shifts between the input and output signals [20]. The cardiac output measured by NICOM has been shown to be highly correlated with that measured by thermodilution, and to be able to track changes of cardiac output accurately [21].

In conclusion, nitroprusside and remifentanil were effective to induce CH in patients undergoing ESS with general anesthesia. During CH, cardiac output was maintained at baseline level in the both groups.

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