Comparison of Labetalol, Nitroglycerine and High Dose Propofol for Induced Hypotension in Functional Endoscopic Sinus Surgery in Massive Nasal Polyposis: A Randomized Trial

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Background: The aim of this study was to assess the quality of the surgical field, amount of blood loss, and duration of surgery following induced hypotension with labetalol, nitroglycerin, and high dose propofol in patients undergoing FESS under general anesthesia.

Methods: One hundred and eight patients scheduled for FESS under general anesthesia were recruited in this randomized trial and were allocated to one of the three study groups: 1) Nitroglycerine (NTG) group: nitroglycerine with a dose of 2-5 μg/kg/min was administered; 2) Labetalol (LAB) group: an IV bolus dose of labetalol (20 mg) was injected at first and then IV infusion of labetalol at a rate of 1-2 mg/min; 3) High dose propofol plus normal saline (0.5-1 ml/min) group. Hemodynamic variables and the amount of bleeding were recorded intraoperatively and the surgeons’ satisfaction was asked following each surgery considering the surgical field quality using a 5-item Likert scale.

Results: The average blood loss (ml) in patients in the LAB group was significantly less than patients in NTG and high dose propofol groups (127 ml vs 198 and 145 ml, respectively) (p-value=0.001) and the surgeons expressed greater satisfaction with the surgical field quality in the LAB group (p-value=0.001).

Conclusion: Labetalol infusion may be a safe and effective method for induction of controlled hypotension to provide a comparatively bloodless field. High dose propofol may be a second choice if labetalol is not available.

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FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS) is currently accepted as a surgical intervention for treatment of refractory chronic rhinosinusitis and other sinus problems [1]. Surgical field visualization is essential to the success of this procedure and to minimize the development of any complication. Bleeding in the surgical field may lead to prolonged duration of operation, defective surgical procedures, and higher operative complications because of insufficient apparent surgical field and unclear critical points resulting in damages to important tissues or organs; this condition can be worse in massive nasal polyposis [2-4]. Several techniques have been proposed to improve the surgical field in sinus surgery, including topical vasoconstrictors, reverse Trendelenburg position, intravenous anesthesia, and induced hypotension [5-6]. Use of hypotensive...
medications is among the methods proposed to create a bloodless field. It is proposed that decreased mean arterial pressure (MAP) as well as lowered blood flow to the mucosal tissue of the nose occurred using these medications [2]. Although vasodilatation, reflex tachycardia and subsequent raised cardiac output may lead to extra local bleeding following administration of pure vasodilators such as sodium nitroprusside or nitroglycerine [6-7]. Furthermore, it was shown that beta-blockers are effective in reduction of local bleeding because of their effects in lowering cardiac output without significant systemic vasodilatation [6,8]. Labetalol is a combined alpha-1 and beta-adrenergic receptor blocking agent; therefore, decreasing systemic vascular resistance accompanied by lowering heart rate cause reducing blood pressure without significantly limiting cardiac output [9]. Few studies have compared the effect of labetalol and nitroglycerin infusion in regard to reducing bleeding and achieving better intraoperative condition in FESS procedure [10]. Therefore, our goal was comparison of the quality of the surgical field, amount of blood loss, and duration of surgery following induced hypotension with labetalol and nitroglycerin compared to high dose propofol in sinus surgery of patients with massive nasal polyposis.

**Methods**

**Study Subjects**

In this prospective double-blinded randomized trial, 108 patients with ASA (American Society of Anesthesiologist) score of I and II between 20 to 60 years old scheduled for FESS were recruited. All patients were first –time candidates for bilateral FESS due to chronic sinusitis with nasal polyposis and duration of symptoms of at least ≥12 weeks. Diagnosis of CRS was confirmed with paranasal sinus CT and amount of sinus opacifications were graded using Lund-Mackay scoring system. All of them had pan sinusitis with Lund Mackay Score 24. We excluded patients with any history of bleeding disorders, known allergy to any of the study drugs, cardiovascular dysfunction such as high blood pressure, any coronary artery or heart valve diseases or heart failure, major hepatic, renal or cerebrovascular disease, severe chronic obstructive pulmonary disease, opium addiction, pregnancy, cystic fibrosis, Sampter's triad, congenital mucociliary problems, severe septal deviation, immune deficiency, and systemic vasculitis and those taking anticoagulation therapy.

**Technical details**

All patients were fasting for 8 hours. After transporting patients to the operating room, a 20-gauge intravenous cannula was inserted for each patient and then standard monitoring, including pulse oximetry (SpO2 monitoring), 5-lead electrocardiography (ECG), and noninvasive blood pressure (NIBP) and capnography (EtCO2 monitoring), were attached to all patients. Premedication before induction of anesthesia was administration of IV fentanyl (2 µg/kg) in addition to midazolam (0.05 mg/kg) and lactated ringer solution (5 ml/kg) in 15 minutes. Induction of general anesthesia was performed with administration of intravenous propofol with a dose of 1.5mg/kg and muscle paralysis was induced by intravenous cisatracurium (0.15 mg/kg). Anesthesia was continued by infusion of propofol (0.1-0.3 mg/kg/min IV infusion) plus nitrous oxide 60% to 70% and oxygen. BIS monitoring was applied and kept between 40 and 60. The patients were mechanically ventilated using the mandatory volume mode to maintain the end-tidal concentration (EtCO2) between 35 and 45 mmHg. Cisatracurium was given for maintenance of muscle relaxation based on using a peripheral nerve stimulator (TOF-Watch, Organon, Dublin, Ireland). During surgery, lactated ringer solution was administered according to maintenance needs and the amount of blood loss. Prior to draping the patient and starting the surgery, each patient received topical anesthesia and vasoconstriction by application of 2ml lignocaine 1% with epinephrine at a dilution of 1 in 100,000 to the nasal mucous membrane to minimize blood loss. Moreover, all patients were kept in the head up position at a level of 30° during the surgery to improve the head and neck venous drainage. The patients were randomly allocated to three groups: 1) nitroglycerine group (NTG): infusion of nitroglycerine with a dose of 2-5 µg/kg/min; 2) labetalol group (LAB): a 20 mg intravenous bolus dose of labetalol was continued by infusion of labetalol at a rate of 1-2 mg/min; 3) high dose propofol plus normal saline group (0.5-1 ml/min). In all groups, the infusion rate of the drugs including labetalol, nitroglycerine and propofol was titrated until the lowest target of mean arterial blood pressure (MAP) between 60-70 mmHg was achieved. In case of MAP<60 mmHg, the infusion rate of the drugs was decreased and if no response was observed, the drug infusion was stopped. For resistant hypotensive state, ephedrine (5-10 mg) was administered and the case was excluded from the study. Moreover, atropine 0.5 mg intravenously was commenced in case of heart rate less than 60 beats/min.

**Variables and outcome measurements**

In all patients, ECG, SpO2, EtCO2, and temperature were monitored continuously and hemodynamic parameters including heart rate (HR), systolic, diastolic and mean arterial pressure were measured. Hemodynamic variables were recorded before induction of anesthesia as baseline, 5 minutes after intubation, at the start of surgery, 5,10, 15, 30, 45, and 60 minutes during the procedure, and at the end of surgery (T0 -T8 respectively). The volume of intraoperative bleeding was
assessed by measuring the suction bottle volume and the weight of blood soaked gauzes consumed during the procedure. At the end of each surgery, the surgeons were asked to rate their satisfaction with surgical field quality using a 5-item Likert scale (1 = poor and 5 = excellent) [11]. Deliberate hypotension was discontinued at 10 minutes left to the end of surgery. Patients received recovery care at post anesthesia care unit (PACU) following surgery. Occurrence of postoperative nausea, vomiting and shivering were recorded.

Blinding and Randomization

The study patients were randomly allocated to three groups. Moreover, all data were collected by an anesthesia resident who was blinded to the study groups. All operations were performed by two surgeons who were not informed about study groups and the content of solutions administered to each patient.

Statistical Methods

Based on our pilot study, 108 patients, 36 patients per group, were needed to find out twenty percent difference between-group in the amount of bleeding from the surgical field with a power of 80% and a significance level of 5%. SPSS version 18 (SPSS, Inc. Chicago, IL, USA) was applied for data analysis. We compared variables between three groups using one way ANOVA, Student’s T test, chi Square test and Fisher’s exact test according to the variables. Repeated measure analysis of variance was applied. Bonferroni post HOC test was used for between-group comparisons.

Table 1 - Comparison of variables between three groups

| Variables                  | Group                                      | P value |
|----------------------------|--------------------------------------------|---------|
|                            | High dose propofol | Labetalol | Nitroglycerin |
| Sex                       | Female| 18(50.0%) | 16(44.4%) | 22(61.1%) | 0.3 |
|                           | Male  | 18(50.0%) | 20(55.6%) | 14(38.9%) |   |
| Age (year)                | 31.9±6.6 | 32.2±5.1 | 31.4±9.2 | 0.8 |
| Duration of surgery (min)| 109.7±17.5 | 99.4±22.2 | 115.8±19.6 | 0.004 |
| Blood loss (ml)           | 145.0±69.1 | 127.3±45.1 | 198.4±104.1 | 0.001 |
| Surgeon’s satisfaction    | 2.7±0.6 | 3.8±0.8 | 2.4±0.6 | 0.001 |
| Duration of anesthesia (min)| 135.4±18.1 | 115.9±23.4 | 123.1±20.7 | 0.001 |
| Recovery time (min)       | 39.1±7.2 | 37.8±9.0 | 38.4±7.7 | 0.91 |

1 Labetalol vs Nitroglycerin (p=0.003)

II Labetalol vs Nitroglycerin (p<0.001); High dose propofol vs Nitroglycerin (p=0.013)

III Labetalol vs Nitroglycerin (p<0.001); Labetalol vs High dose propofol (p<0.001)

IV Labetalol vs Nitroglycerin (p<0.001); Labetalol vs High dose propofol (p<0.001)

V Labetalol vs Nitroglycerin (p=0.81); Labetalol vs High dose propofol (p=0.78)

Results

A total of 108 patients were finally enrolled in this study. Age, sex, weight, and ASA class were comparable (Table 1). Anesthesia and surgery duration was significantly shorter in LAB group than NTG and high-propofol groups. The average blood loss (ml) in patients in the LAB group was significantly less than patients in NTG and high-propofol groups (127 ml vs 198 and 145 ml, respectively) (p-value=0.001). The surgeons expressed more satisfaction with surgical field quality in LAB group. The mean anesthesia time was also significantly shorter in patients in the LAB group compared to patients in NTG and high dose propofol groups (Table 1).

Systolic, diastolic, and mean blood pressure measured at baseline and different intervals were comparable between the three groups. The MAP of the patients in all groups was in a favorable range after 5 minutes after the start of the surgery (60-70 mmHg). The mean intraoperative HR in LAB patients decreased more than patients in the other groups during anesthesia (p<0.001) (Figure 1).

Eight patients of NTG group and four patients of LAB and control groups showed postoperative nausea and vomiting but the difference was not significant (p=0.35). Similarly, the number of patients who experienced postoperative shivering was not statistically different between groups (8, 9, and 9 in high dose propofol, LAB and NTG groups, respectively, p=0.89). Finally, the duration of stay in the post anesthesia care unit was comparable in all groups (p=0.91).
Discussion

In this study, we assessed the surgical field quality, amount of blood loss, and duration of surgery following controlled hypotension with labetalol, nitroglycerin, and high dose propofol in 108 patients undergoing FESS under general anesthesia. We observed that the mean intraoperative blood loss was significantly less and the duration of surgery was significantly shorter in patients in the LAB group than patients in NTG and high dose propofol groups. Moreover, surgeons were more satisfied with the surgical field quality in the LAB group.

Surgical bleeding is related to tissue blood circulation that is dependent to arterial and venous pressure as well as regional capillary circulation. The major contributing factor in operative field oozing in sinus endoscopic surgery is capillary over-bleeding which will be reduced by induced controlled hypotension as well as application of topical vasoconstriction [10]. Low doses of nitroglycerine cause a marked dilating effect on the veins and a weaker effect on the arterioles, hence, reducing both venous return and cardiac output. High doses of nitroglycerine can induce hypotension through arterial dilatation. Peripheral vasodilation associated with NTG may increase the amount of bleeding and oozing in the surgical field [12]. We showed that NTG infusion is not a good choice for inducing controlled hypotension during FESS because the amount of surgical bleeding and the surgeons’ satisfaction with the field quality in the TNG group were improved a little, but the difference was not significant in comparison with high dose propofol. As predicted, patients in the NTG group had higher mean heart rate compared to patients in LAB and propofol groups that can be explained by reflex tachycardia. EL-Shmaa et al designed a similar study to compare nitroglycerine and labetalol for induction of controlled hypotension in FESS and showed that nitroglycerine was not as good as labetalol for providing optimum operative conditions [10]. Our results are in agreement with the findings of EL-Shmaa study, but we also had a high dose propofol group in which controlled hypotension was induced by propofol infusion alone. In other words, NTG infusion cannot provide more favorable surgical conditions compared to high dose propofol infusion during FESS. Labetalol has been used for controlled hypotension in combination with intravenous or inhalation anesthetics during various surgical procedures. Labetalol is a combined alpha- and beta-receptor blocker showing vasodilation in combination with controlled heart rate [5]. Reduction of peripheral vascular resistance via alpha blocking effect in peripheral arteries and inhibited reflex sympathetic stimulation by beta-blockade effect keeps the heart rate stable while cardiac output is preserved; therefore, it causes reducing the amount of blood loss in rhinoplasty, FESS, and orthognathic surgeries [5,13-14]. Administration of propofol reduced systolic blood pressure via a lower decrease in systemic vascular resistance and blunt the sympathetic response during periods of surgical stimulation. Propofol is associated with reduced cerebral circulation and arterial blood volume in head and neck areas particularly in the ethmoid, sphenoid, and frontal sinuses will be decreased so the surgical field will be cleaner [15]. However, more recent studies have shown that routine doses of propofol cannot significantly improve surgical field bleeding without concomitant use of remifentanil [16-17]. Therefore, we decided to use high dose propofol as a third method to induce hypotension and to compare the results with two other methods. In our study, all groups had an acceptable MAP (mild to moderate controlled hypotension) during surgery. However, with respect to the amount of bleeding and the surgeons’ satisfaction with the surgical field, it seems that keeping MAP in the range of mild to moderate
hypotension is not sufficient for providing an ideal bloodless operative field. Consistent with our results, a study by Jacobi showed that the surgical condition and amount of blood loss in endoscopic sinus surgeries will not improve by moderately controlled hypotension with a vasodilator like sodium nitroprusside [7].

In our study, the mean blood loss (ml) in LAB group was significantly less than NTG group while there was no significant difference between LAB group and high dose propofol. It has been shown that propofol infusion reduces microvascular density and capillary blood flow significantly [18]. Although all three groups received propofol infusion, one of the groups received high dose propofol that showed its obvious effects on bleeding control and surgeon’s satisfaction. Due to the magnification of the surgical field by the endoscope camera lens, even a slight difference in the amount of bleeding in the surgical field can lead to a significant difference in the surgical vision and the surgeon’s satisfaction with the field of surgery, while the difference in the amount of intraoperative bleeding which is estimated by measuring the volume of liquid inside the suction bottle and weighing bloody gauzes may not be clinically significant between groups. Finally, providing a blood free surgical field can decrease the time needed for suctioning and clearing the field of surgery, hence reducing the total duration of surgery, which was confirmed by the results of this study. Moreover, the mean duration of anesthesia in patients receiving LAB was significantly shorter than patients in NTG and high dose propofol groups, which could be due to differences in the mean surgical time between the study groups or administration of more anesthetics in the propofol group to achieve the target range of MAP.

In this study, we did not observe any undesirable side effects in patients following controlled hypotension intraoperatively and in post anesthesia care unit. There are several limitations to our study. First, we chose a MAP of 60-70 mmHg as a favorable target for controlled hypotension. If profound hypotension was induced, the results could be different. Second, we did not measure stress hormones or the concentration of catecholamines in our patients, so the adequacy of the anesthetic technique for suppressing the stress response during the surgical procedure is not clear. Third, we did not use cerebral oximetry to monitor the adequacy of cerebral perfusion during controlled hypotension due to limitation of resources in our center.

**Conclusion**

We showed that labetalol infusion might be a safe and effective method for induction of controlled hypotension to provide a bloodless field. In our study, labetalol infusion was superior to nitroglycerin or high dose propofol in improvement of the surgical field visualization and surgeons’ satisfaction. A shorter duration of surgery and anesthesia and less tachycardia were other advantages of this technique. High dose propofol may be the second choice if labetalol is not available.

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**Ethical Standards**

The authors assert that all procedures contributing to this work comply with the ethical standards of Tehran University of Medical Sciences guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Moreover, this study was registered in IRCT.IR (Irc ID: IRCT201511295225N6) and written informed consent was obtained from all the patients.

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