Comparative Study Between the Efficacy of Oral Verapamil and Bisoprolol on Reduction of Intraoperative Bleeding during Endoscopic Sinus Surgery under General Anesthesia

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Abstract

Background:
Intraoperative bleeding is thought to be a significant barrier to endoscopic vision. Blood obstructs the surgical field's anatomy and stains the endoscope lens, making visibility more challenging. The likelihood of consequences, such as brain injuries, orbital or optic nerve damage, and catastrophic haemorrhage from significant arteries, is increased in this circumstance.
Objectives:
To investigate the effects of adding verapamil and bisoprolol to general anaesthetic to reduce heart rate and blood loss at endoscopic sinus surgery, to explore the surgeon's evaluation of the surgical field and hemodynamics, and to investigate the effects of adding verapamil and diltiazem to general anaesthetic to investigate serum cortisol and norepinephrine levels at endoscopic sinus surgeries.
Patients and methods:
This quasi-experimental investigation was conducted at Assiut University Hospital. A convenience sample of 135 adult patients, both males and females, was divided into three equal groups: the control group (45 patients), who were given a placebo orally (PO) three hours before surgery; the Bisoprolol group (45 patients), who were given Bisoprolol 10 mg PO preoperatively; and the verapamil group (45 patients), who were given 80 mg PO of verapamil three hours before surgery. The primary goal was to determine how adding oral verapamil or Bisoprolol to general anaesthesia affected intraoperative hemodynamics and blood loss during endoscopic sinus surgery. The secondary goal was to determine how adding oral verapamil or Bisoprolol to general anaesthetic affected serum cortisol and norepinephrine levels throughout endoscopic sinus surgeries and the surgeon's evaluation of the surgical field.
Results:
The three investigated groups showed statistically substantial differences in the mean heart rate, mean systolic blood pressure, and blood loss at various intraoperative times. Groups 1 and 2 ($p< 0.001$), 2 and 3 ($p <0.001$), and 1 and 3 ($p <0.001$) all showed statistically substantial differences.
Conclusion: Verapamil and Bisoprolol are reliable and secure medications for this use. However, Bisoprolol was superior since it allowed for ideal surgical conditions while slightly lowering blood pressure. Additional benefits included decreased intraoperative bleeding and tachycardia during the procedure.
Keywords:
Verapamil, reduction haemorrhage , endoscopic sinus surgery under general anaesthesia, and Bisoprolol.

Background

Intraoperative haemorrhage is thought to be a significant barrier to endoscopic vision. Blood obscures the surgical field's anatomy and contaminates the endoscope lens, making visibility more challenging. The likelihood of consequences, such as brain injury, orbital or optic nerve damage, and catastrophic haemorrhage from major arteries, is increased in this circumstance (e.g., internal carotid artery)[1].

To achieve a good bloodless surgical field, controlled hypotension has been employed to decrease haemorrhage and blood transfusion needs. The physiological process that results in hypotensive anaesthesia is a built-in defense mechanism. Blood pressure decreases when there is severe bleeding. This decrease causes the bleeding to lessen or stop, the blood pressure to stabilize, and the patient to recover. In light of this, lowering the patient's blood pressure during surgery may help to lessen total bleeding. The operational circumstances in the surgical field are better since bleeding is also decreased [2].

Beta-blockers counteract sympathetic nerve stimulation and the effects of circulating catecholamines at beta-adrenoceptors found throughout the body. The heart (and kidney) mostly has beta1 receptors, while the lung, peripheral blood arteries, and skeletal muscle primarily contain beta2 receptors 3. Recently, new substances and methods have been tested to see whether they may effectively lower blood pressure without affecting the perfusion of essential organs.

I. Materials and Methods

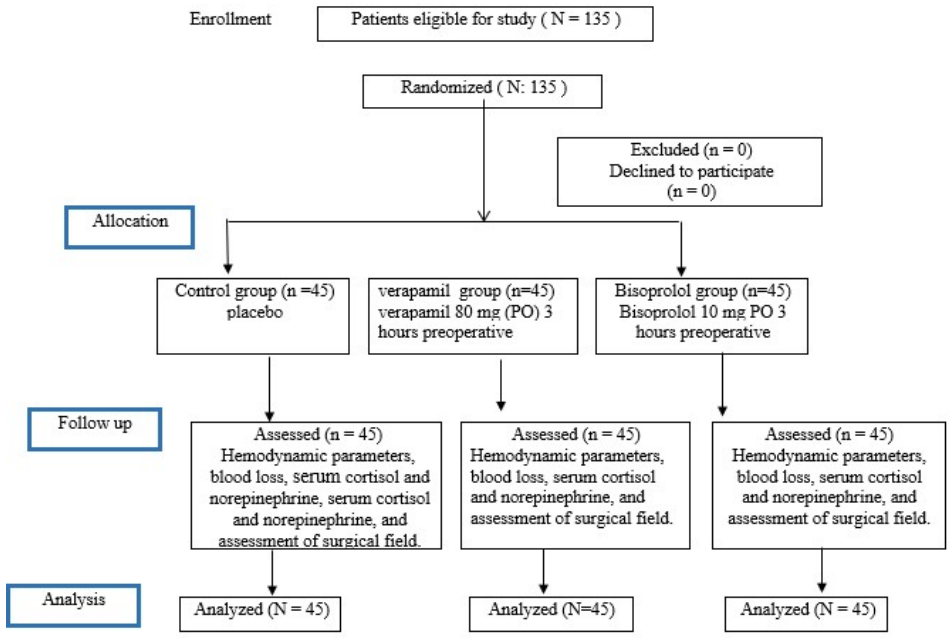
This randomized controlled trial was conducted at the ENT surgery department of the Assiut University Hospital in Egypt between October 2020 and April 202. The study was examined and authorized by the medical school's ethics committee at Assiut University in Egypt (IRB no. 17101109), and the study was registered on ClinicalTrials.gov/ NCT04356196. This study adheres to the Consort guidelines, and as a result, it was carried out in compliance with the Declaration of Helsinki's ethical principles. The primary outcome was the impact of adding oral verapamil or bisoprolol to general anaesthetic on intraoperative hemodynamics; the secondary outcomes were the effects of adding oral verapamil or bisoprolol to general anaesthesia on serum cortisol and adrenaline during endoscopic sinus surgery and the surgeon's evaluation of the surgical field regarding blood loss. Aged 18 years or older and hemodynamically stable were the inclusion criteria. Any hypertensive patient receiving regular therapies other than verapamil or bisoprolol, any calcium channel blocker contraindication due to AV conduction deficiencies (2nd and 3rd degree AV block), sick sinus disorder, wolf-Parkinson-White Disorder, a history of congestive heart failure, patients receiving long-term ß-blocker therapy, and patients who had an allergy to any of the study medication were excluded.

1.1. Research Hypothesis

With Bisoprolol, better heart rate control and decreased intra-operative haemorrhage and tachycardia during the procedure were attained.

2.2. Sample Size

G*Power 3 software (Faul et al., 2007) was used to calculate the sample size. An estimated minimum sample of 135 patients will be needed. The sample will be split into three groups: the control group (45 patients), which received a placebo oral solution (PO) three hours before the procedure; the bisoprolol group (45 patients), who got a 10 mg PO dose of bisoprolol.; and the verapamil group (45 patients) were given 80 mg PO of verapamil three hours before surgery, With an error probability of 0.05 and 80% power on a one-tailed test, 3 hours preoperatively were required to detect an influence size of 0.2 in the percentage of blood loss levels postoperatively [6].



2.3. Procedure

On the day of enrollment, baseline descriptive data were collected from the patient, the patient's family, and the patient's medical records. This information includes age, sex, and pre-existing comorbidities like diabetes, coronary artery illness, asthma, peripheral vascular illness, renal failure, psychiatric illness, musculoskeletal disease, and others. Laboratory baseline data were recorded, including measurements of serum cortisol and norepinephrine. Three hours before surgery, the Verapamil group (45 patients) got 80 mg of verapamil orally (PO), the Bisoprolol group (45 patients) received 10 mg of Bisoprolol orally (PO), and the Control group (45 patients) received a placebo.

In the trial, hemodynamic parameters such as heart rate (HR), systolic blood pressure (SBP), median blood pressure (MBP), diastolic blood pressure (DBP), end-tidal CO2 (CO2), arterial oxygen saturation (SaO2), and operation time and predicted blood loss were monitored hourly.

2.4. Safety

To lessen the possibility of hypotension or other adverse effects after discharge, the patient was retained in the ICU for surveillance within 24 hours after the study medication's termination. Before being discharged to the ward, the study medication was stopped if the blood pressure objective was achieved for more than 24 hours without needing IV vasopressors. The patient's receipt of a study medication was disclosed to the acceptance team at the time of release. The medical and nursing personnel were instructed to contact a physician investigator if the patient had hypotension within 24 hours of being released from the intensive care unit (defined as SBP< 90 mmHg).

3. Results

One hundred thirty-five patients who underwent endoscopic sinus surgery were assessed per the qualifying requirements for potential inclusion in the research, which comprised 135 patients. The process for patient selection and group composition is shown in **Figure 1**.

Preoperative Investigations:

The three groups under study had median cortisol levels of 8.7 ±0.9, 8.6± 1.3, and 8.8 ±0.9, respectively. There was no statistically substantial variation regarding

cortisol between the three study groups. The mean adrenaline levels between the three study groups were 443.2± 53.9, 443.6± 46.9, and 443.3 ±49.7. The three study groups had no statistically substantial variation in the adrenaline levels. The three groups under study had median Hb of 13.6 ± 1.1, 13.5± 1.2, and 13.8± 1.0, respectively. The three study groups had no statistically substantial variation in Hb levels. The median platelet between the three groups under study was 212.8 ± 14.1, 214.5 ± 16.3, and 214.6± 14.9. There was no statistically substantial variation regarding platelets between the three study groups. The three groups under study had mean PTs of 12.0± 0.8, 12.1± 0.7, and 11.9± 0.8, respectively. In terms of PT, there was no statistically substantial variation between the three groups that were examined. **(Table 1).**

Table 1: Preoperative investigations among the three studied groups

Variable	Control group (n= 45)	Verapamil group (n= 45)	Bisoprolol group (n=45)	P value
Cortisol (µg/dL)	8.7± 0.9	8.6± 1.3	8.8± 0.9	0.813
Adrenaline (mcg/ml)	443.2± 53.9	443.6± 46.9	443.3± 49.7	0.999
Hb (g/dL)	13.6± 1.1	13.5± 1.2	13.8± 1.0	0.629
Platelet ($x10^3$) platelets per microliter of blood	212.8± 14.1	214.5± 16.3	214.6± 14.9	0.815
PT (sec.)	12.0± 0.8	12.1± 0.7	11.9± 0.8	0.966

ANOVA; *p is significant at <0.05

The three study groups' median heart rates differed statistically significantly at the beginning of the study. The three groups under study showed statistically substantial differences in median heart rates during induction. However, there was a statistically significant variation in the median heart rate between the three groups under study at various intraoperative times (5, 15, 30, 45, 60, 90, 120, and 150 minutes). By using a post-hoc test, the differences between groups 1 and 2 ($p<0.001$), 2 and 3 ($p<0.001$), and 1 and 3 ($p<0.001$) were all statistically substantial **(Table 2).**

Table 2: Heart rate baseline and intraoperative among the three studied groups

Variable	Control group (n= 45)	Verapamil group (n= 45)	Bisoprolol group (n=45)	P value
HR baseline	104.4± 2.5	69.2± 1.8	58.9± 1.6	**<0.001***
HR induction	107.4± 1.7	68.2± 1.9	57.1± 2.4	**<0.001***
HR 5 min	112.5± 1.8	67.2± 1.5	53.9± 2.7	**<0.001***
HR 15 min	107.6± 4.3	68.1± 1.4	54.6± 3.3	**<0.001***
HR 30 min	113.2± 2.3	67.9± 1.6	56.4± 2.4	**<0.001***
HR 45 min	117.6± 1.8	64.6± 2.1	56.1± 2.6	**<0.001***
HR 60 min	116.8± 2.1	66.9± 2.3	58.5± 5.6	**<0.001***
HR 90 min	115.7± 3.3	66.5± 1.9	56.2± 2.2	**<0.001***
HR 120 min	114.9± 2.9	64.0± 0.8	59.4± 4.5	**<0.001***
HR 150 min	109.4± 5.7	66.8± 2.2	60.6± 4.9	**<0.001***

Kruskal Wallis test; *p is significant at <0.05

At the beginning of the study, there was no statistically substantial variation in the median systolic blood pressure between the three groups. The three groups under study did not vary statistically significantly regarding median systolic blood pressure

during induction. There was a statistically substantial variation in the median systolic blood pressure between the three study groups at various intraoperative times (5, 15, 30, 45, 60, 90, 120, 150 minutes). By using a post-hoc test, the differences between groups 1 and 2 (p<0.001), 2 and 3 (p<0.001), and 1 and 3 (p<0.001) were all statistically substantial **(Table 3).**

Table 3: Systolic blood pressure in the three groups under investigation

Variable	Control group (n= 45) (Mean ± SD)	Verapamil group (n= 45)	Bisoprolol group (n= 45)	P value
SBP baseline	127.4± 1.7	132.2± 1.7	135.5± 3.2	0.511
SBP induction	132.1± 2.0	135.7± 1.8	125.2± 3.1	0.304
SBP 5 min	129.6± 3.4	96.8± 1.9	85.3± 3.4	**<0.001***
SBP 15 min	133.1± 1.9	95.4± 3.3	84.9± 3.1	**<0.001***
SBP 30 min	130.5± 1.7	94.9± 2.8	84.6± 3.2	**<0.001***
SBP 45 min	130.3± 2.4	95.0± 3.4	85.4± 2.7	**<0.001***
SBP 60 min	128.9± 2.6	94.8± 3.2	84.6± 3.2	**<0.001***
SBP 90 min	131.7± 2.9	95.4± 2.9	84.5± 3.1	**<0.001***
SBP 120 min	131.8± 3.6	94.9± 2.9	85.0± 3.2	**<0.001***
SBP 150 min	131.5± 1.5	95.4± 3.2	84.0± 3.1	**<0.001***

Kruskal Wallis test; *p is significant at <0.05

The mean blood loss was 160.2± 37.6, 122.4± 31.1, and 96.9± 26.0 mL among the three study groups. There was a statistically substantial variation regarding blood loss between the three study groups. According to the post-hoc test, there was a statistically significant variation between groups 1 and 2, 2 and 3, and 1 and 3 (p<0.001, p<0.001, and p<0.001, respectively). 11% of group 3 members were in grade 1. There were 11% and 60% grade 2 among groups 2 and 3. There were 57.8%, 66.7%, and 28.9% grade 3 among groups 1, 2, and 3, respectively. There were 37.8% and 22% grade 4 among groups 1 and 2, respectively. There was 4% grade 5 among group 1. Between the three study groups, there was a statistically substantial variation in the bleeding scale (Table 4).

Table 4: Blood loss among the three study groups

Variable		Control group (n= 45)	Verapamil group (n= 45)	Bisoprolol group (n= 45)	P value
Blood loss	Mean ± SD	160.2± 37.6	122.4± 31.1	96.9± 26.0	**<0.001***
Bleeding scale	Grade 1, n (%)	0 (0)	0 (0)	5 (11.1)	**<0.001***
	Grade 2, n (%)	0 (0)	5 (11.1)	27 (60)	
	Grade 3, n (%)	26 (57.8)	30 (66.7)	13 (28.9)	
	Grade 4, n (%)	17 (37.8)	10 (22.2)	0 (0)	
	Grade 5, n (%)	2 (4.4)	0 (0)	0 (0)	

ANOVA; Fisher Exact test; *p is significant at <0.05

There were statistically substantial differences in HR, SBP, and DBP between the three groups under study. According to the post-hoc test, there was a statistically significant variation between groups 1 and 2, 2 and 3, and 1 and 3 (p<0.001, p<0.001, and p<0.001, respectively). Regarding SaO2, there was no statistically substantial variation between the three study groups (Table 5).

The three groups under study differed statistically significantly regarding postoperative cortisol and adrenaline levels. By using a post-hoc test, the differences between groups 1 and 2 (p<0.001), 2 and 3

(p<0.001), and 1 and 3 (p<0.001) were all statistically substantial (Table 6).

Table 5: Postoperative vital signs among the three studied groups

Variable	Control group (n=45)	Verapamil group (n= 45)	Bisoprolol group (n= 45)	P value
HR	100.5± 6.1	67.6± 1.7	57.6± 4.8	**<0.001***
Systolic BP	105.9± 8.7	87.3± 7.6	82.5± 4.8	**<0.001***
Diastolic BP	81.3± 7.1	75.2± 2.9	64.9± 3.5	**<0.001***
SaO2	97.9± 1.4	97.9± 1.1	98.2± 1.6	0.563

Kruskal Wallis test; *p is significant at <0.05

Table 6: Postoperative Cortisol and adrenaline among the three studied groups

Variable	Control group (n= 45)	Verapamil group (n= 45)	Bisoprolol group (n= 45)	P value
Cortisol	11.6± 0.9	10.9± 1.2	10.4± 0.9	**<0.001***
Adrenaline	610.7± 50.9	542.8± 46.3	511.3± 51.7	**<0.001***

ANOVA; *p is significant at <0.05

Discussion

This comparative clinical research examined and contrasted the hypotensive impact of verapamil and Bisoprolol in 135 ASA Grade I and II patients aged 18 to 60 years who had FESS under general anaesthetic. Our study results found no statistical differences between the included groups in terms of the age of the subjects. The mean age of the verapamil group was 41.8± 12.1, while that of Bisoprolol was 37.4± 11.4 years. Using an average category scale (ACS) of 0-5, the surgeon evaluated the patient's surgical status, with a score of 2-3 being excellent. Our study results found statistical differences between the groups regarding the SBP of the included subjects. The median basal values of Bisoprolol were 135.5± 3.2 mm Hg. This is explained by the mechanism of hypotension brought on by each FESS, which is often utilized for common ailments like rhino- and polypus sinusitis.
Similarly, Chakraborty found that the group receiving Bisoprolol had a more significant attenuation of systolic blood pressure. However, the variation was not statistically substantial at other periods than immediately after induction (p-value< 0.001)[4].

Our study results found a statistical difference between included groups regarding the DBP of included subjects. The median basal DBP values of verapamil and Bisoprolol group were 84.7± 3.3 mm Hg and 84.8± 3.5 mm Hg respectively.

The Chakraborty investigation discovered that the Bisoprolol-treated group had a more significant median arterial blood pressure attenuation. However, the variation was not statistically substantial (p > 0.05) at other periods than shortly after intubation. This might be explained by the fact that bisoprolol and verapamil immediately impact median arterial blood pressure soon after intubation (drug previously administered before that), with bisoprolol having a more prominent effect [5].
Our results mirror those of Vehapoglu [6] regarding trends in heart rate, systolic BP and diastolic BP. Similarly, Son et al. discovered that heart rates were considerably reduced in the Bisoprolol groups following tracheal intubation compared to the verapamil groups [7]. The beta-adrenergic blocking properties of bisoprolol are thought to be responsible for this decrease in heart rates in the ESM

group. Verapamil relieves blood vessel tension, which reduces the heart's workload. To regulate the heart, it also increases the amount of blood and oxygen delivered to the organ [8].

According to the findings of our investigation, there were statistical variations between the included groups as regards the participants' blood loss. The mean blood loss of the verapamil and Bisoprolol group were 122.4± 31.1 mL and 96.9± 26.0 mL, respectively. As a consequence of Bisoprolol's b-blockade, unopposed adrenergic actions during Bisoprolol-induced hypotension induce arterioles and pre-capillary sphincters to contract, which reduces bleeding at the surgical site and improves the surgical field's quality 9. This might cause vasodilation, increasing the leaking at the surgical site. One potential contributory cause is reflex tachycardia [10].

Our study results found that regarding the surgical duration of included subjects, there was a statistical difference between included groups. The median surgical duration in the NTG group was 104.0± 27.6 minutes, while 92.4± 17.9 minutes in the ESM group. Our surgical duration results are similar to Srivastava's[11] results. Nair claimed that the drop-in heart rate below 60 beats per minute caused by premedication with B blockers results in improved surgical circumstances during FESS. Inducing hypotension encourages the release of endogenous catecholamines [12].

Conclusion:

Due to the improvement in the surgical state, controlled hypotension is a crucial technique during FESS. The method is straightforward, secure, and simple to use. Verapamil and bisoprolol are both reliable and safe medications for this use. However, Bisoprolol was superior since it allowed for ideal surgical conditions while slightly lowering blood pressure. Additional benefits included decreased intraoperative bleeding and tachycardia during the procedure.

References:

1. Gustavo H, Ricardo L, Carrau C. Vascular Pedicle Nasoseptal Flap. Laryngoscope. 2006;116(10):1882–1886.
2. Degoute CS, Ray MJ, Manchon M, Dubreuil C, Banssillon V. Remifentanil and controlled hypotension: comparison with nitroprusside or Bisoprolol during tympanoplasty. Can J Anaesth. 2001;48(1):20.
3. Khan MG. Beta-blockers. In: Cardiac Drug Therapy. 7th ed. New Jersey: Humana Press Inc; 2007. p. 2.
4. Chakraborty N, Roy S, Sur D, Biswas A, Bhattacharya D, Adhikari A. Comparison between Bisoprolol and verapamil in attenuation of cardiovascular stress response to laryngoscopy and endotracheal intubation in elective surgery. Asian J Med Sci. 2021;12(7):64–68.
5. Manhas A, Jamwal S, Gupta S, Mehta N. Attenuation of the Pressor Response to Laryngoscopy and Endotracheal Intubation with Different Intravenous Doses of Bisoprolol. Int J Med Res Prof. 2016;2(5):137-140.
6. Vehapoglu A, Ozgurhan G, Demir A, Uzuner S, Nursoy M, Turkmen S, et al. Hematological indices for differential diagnosis of Beta thalassemia trait and iron deficiency anemia. Anemia. 2014;2014:576738.
7. Son Y, Ha J, Choi D, Cheong Y, Yoon J. Comparison of Verapamil and Bisoprolol for Controlling the Blood Pressure and Heart Rate to Tracheal Intubation According to the Different Anesthetic Induction Agents. Korean J Anesthesiol. 1999;37(2):221–226.
8. Routray S, Mishra D, Routray D, Nanda K. Effect of verapamil as an adjuvant to levobupivacaine in supraclavicular brachial plexus block. Anesth Essays Res. 2017;11(3):656-659.
9. Mikawa K, Nishina K, Maekawa N, Obara H. Comparison of Nicardipine,

Diltiazem, and Verapamil for Controlling the Cardiovascular Responses to Tracheal Intubation. Surv Anesthesiol. 1997;41(2):91-94.

10. Cardesín A, Pontes C, Rosell R, Escamilla Y, Marco J, Escobar MJ, et al. Hypotensive anaesthesia and bleeding during endoscopic sinus surgery: an observational study. Eur Arch Otorhinolaryngol. 2013;271(6):1505–1511.
11. Srivastava U, Dupargude A, Kumar D, Joshi K, Gupta A. Controlled hypotension for functional endoscopic sinus surgery: comparison of Bisoprolol and nitroglycerine. Indian J Otolaryngol Head Neck Surg. 2013;65(2):440–444.
12. Nair S, Collins M, Hung P, Rees G, Close D, Wormald P. The Effect of β-Blocker Premedication on the Surgical Field during Endoscopic Sinus Surgery. Laryngoscope. 2004;114(6):1042–1046.