Background: The success of functional endoscopic sinus surgery (FESS) depends on visual clarity of the surgical field, through the endoscope. The objective of this double-blind, randomized, controlled study was to determine if a pre-operative dose of bisoprolol (2.5 mg) would reduce the bleeding during FESS and improve the visualization of the operative field.

Materials and Methods: Thirty American Society of Anesthesiologists I or II patients, scheduled for FESS were randomized to receive either a placebo (Group A) or 2.5 mg of bisoprolol (Group B) 90 min prior to the surgery. All the patients received standard anesthesia and monitoring. The aim was to maintain the mean arterial pressure (MAP) of 60-70 mmHg, by titrating dose of isoflurane and fentanyl. The concentration of isoflurane used was recorded every 15 min. At the end of the surgery, the volume of blood loss was measured and the surgeon was asked to grade the operative field as per the Fromme-Boezaart Scale.

Result: The blood loss was significantly ($P < 0.0001$) more in the control group (398.67 ± 228.79 ml) as compared with that in the bisoprolol group (110.67 ± 45.35 ml). The surgical field was graded better in those who received bisoprolol as compared with those in the control group ($P = 0.0001$). The volume percent of isoflurane and the dose of fentanyl used was significantly lower in those who received bisoprolol. During the operative period, the MAPs were 70.0 ± 2.7 (Group A) and 62.6 ± 3.6 mmHg (Group B) and the heart rate was 99.8 ± 5.0/min (Group A) and 69.2 ± 4.4/min (Group B). These differences were statistically significant ($P < 0.001$).

Conclusion: This clinical trial has demonstrated that administration of a single pre-operative dose of bisoprolol (2.5 mg) can significantly reduce the blood loss during FESS and improve the visualization of the operating field.

Key words: Beta-blocker, bisoprolol, blood loss, functional endoscopic sinus surgery, surgical field
Materials and Methods

This double-blind, randomized, controlled study was approved by the Institutional Research and Ethics Committee. All adult, American Society of Anesthesiologists (ASA) physical status I and II patients, scheduled for FESS, were eligible to participate in this study. Patients with hypertension, asthma, bleeding disorders and those on anti-platelet or anti-hypertensive medications were excluded. During the pre-operative evaluation, the study details were explained to the patients and an informed consent was obtained. A total of 30 subjects consented and as per the serially-labeled, sealed envelope, received the study drug (bisoprolol fumarate 2.5 mg or a placebo) orally with a sip of water, 90 min before the surgery.

The anesthesiologist taking care of the patient was blinded to the randomization. The anesthetic management of all the subjects was similar. Standard monitoring included electrocardiography, non-invasive blood pressure, pulse oximeter and end-tidal CO₂. Anesthesia was induced with midazolam 1 mg, fentanyl 1-2 μg/kg, thiopentone 4.5 mg/kg and vecuronium 0.1 mg/kg and maintained on nitrous-oxide (60%), oxygen (40%) and isoflurane. The trachea was intubated with a suitable sized endotracheal tube and all patients received intravenous fluid at 4 ml/kg/h. Patient was positioned supine with the head elevated to about 30°. The surgeon infiltrated the nasal mucosa using 2% lidocaine with epinephrine (1:200,000). The plan was to maintain a mean arterial pressure (MAP) around 60-70 mmHg during the surgery. It was left to the anesthesiologist’s clinical judgment to adjust the concentration of isoflurane and the dose of fentanyl. Dexamethasone (4 mg), immediately after induction of anesthesia and ondansetron (4 mg), half an hour before the end of the surgery was administered as antiemetic. At the end of the surgery, the residual neuromuscular blockade was reversed with a standard dose of neostigmine and atropine. All the subjects were observed in the post-anesthesia care unit (PACU) for an hour and in the ward overnight. In the PACU, the hemoglobin level was measured in all the patients.

The percentage of isoflurane administered and the total gas flow was recorded every 15 min. The volume of blood lost during surgery was measured by recording the volume in the suction bottle and counting the number of cotton strips used during surgery. A fully soaked cotton strip was estimated to contain 5 ml of blood and a partially soaked one as containing 2.5 ml. Immediately after the surgery, the surgeon was asked about his perception of the operating conditions and to grade the surgical field during the surgery, using the Fromme-Boezaart scale.

### Fromme-Boezaart surgical field grading[^3,4]

- **Grade 0**: No bleeding
- **Grade 1**: Slight bleeding. No suctioning of blood required
- **Grade 2**: Slight bleeding. Occasional suctioning required. Bleeding does not threaten surgical field
- **Grade 3**: Slight bleeding. Frequent suctioning required. Bleeding threatens surgical field a few seconds after suction is removed
- **Grade 4**: Moderate bleeding. Frequent suctioning required. Bleeding threatens surgical field immediately after suction is removed
- **Grade 5**: Severe bleeding. Constant suctioning required. Bleeding appears faster than can be removed by suction. Surgical field threatened and surgery not possible

### Statistics

#### Calculation of sample size

A pilot study was carried out on 16 patients, with 8 of them receiving bisoprolol fumarate 2.5 mg as premedication while the others acted as controls. The amount of blood loss in the study group was 146 ± 29.73 ml while it was 251.25 ± 90.73 ml in the control group. To demonstrate a reduction in blood loss of 100 ml with a standard deviation of 60 ml, and α error of 5% and a β error of 20%, a sample size of 15 in each arm was calculated.

#### Randomization

A computer-generated block randomization list, with 10 patients in each block, was drawn up prior to commencement of the study. Serially numbered sealed envelopes contained the study medication as per the randomization. The envelope was opened just before the study drug was to be administered.

#### Statistical analysis

All continuous variables were compared using the Student’s t-test. A *P* < 0.05 was considered to be statistically significant. The statistical analysis was carried out using the statistical package for the social sciences (SPSS 11.0.1; SPSS Inc. April 2002).

#### Calculation of isoflurane

Avagadro’s law states that 1 g-molecular weight of any gas would occupy 22.4 L at standard temperature and pressure.

Therefore, 184 g of isoflurane vapor would occupy 22.4 L.

1 g of isoflurane would occupy – 22,400/184 = 121.73 ml.

Since, the density of isoflurane is 1.495.

A total volume of 1 ml of liquid isoflurane would provide 182 ml (121.73 × 1.495) of vapor.

The concentration of isoflurane delivered were noted every 15 min and averaged over the duration of surgery. If the
average concentration delivered is X% and the fresh gas flow is Y ml/min, then the volume of isoflurane delivered would be Y × X/100 ml/min.

A total volume of isoflurane vapor delivered would be Y × X/100 ml/min × time. Since, 182 ml of vapor would be delivered by 1 ml of liquid isoflurane Y × X/100 ml of vapor would be delivered by Y × X/18,200 ml of liquid isoflurane. Therefore, total volume of liquid isoflurane used would be Y × X/18,200 × time (ml).

Results

Thirty, ASA physical status I or II patients, scheduled for FESS were consented for the study and randomly allocated into either Group A (control) or Group B (bisoprolol). The age, gender, body weight and the pre-operative hemoglobin of the subjects were comparable between the two groups [Table 1].

Blood loss and surgical field

The average blood loss was significantly more in the control group (398.67 ± 228.79 ml) as compared to that in the bisoprolol group (110.67 ± 45.35 ml) [Table 2]. The post-operative hemoglobin was significantly lower in the control group as compared with the bisoprolol group and this was reflected in the difference between the pre- and post-operative hemoglobin values [Table 2]. Although the duration of surgery was shorter in the bisoprolol group there was no statistical difference.

At the end of the surgery, the surgical field was graded by the surgeon, based on the amount of bleeding and visibility of the surgical field, as per the Fromme-Boezaart grading scale. The surgical field was graded better in those who received bisoprolol as compared with those in the control group. This was statistically significant [Table 3].

Hemodynamic parameters

Prior to induction of anesthesia, the MAP was similar between the two groups, but the heart rate was significantly lower in those who received bisoprolol. The rise in blood pressure and heart rate, due to the sympathetic stimulation of intubation and the response to the infiltration of the vasoconstrictor into the nasal mucosa, was more pronounced in the control group.

The heart rate in the control group was 99.8 ± 5.0/min as compared with 69.2 ± 4.4/min, in the bisoprolol group [Figure 1]. After the initial surge in blood pressure, during the operative period, the MAPs were 70.0 ± 2.7 and 62.6 ± 3.6 mmHg in the control and the bisoprolol groups, respectively [Figure 2]. The differences of both these parameters were statistically significant (P = 0.001).

In one patient, while the surgeon was infiltrating the nasal mucosa with 2% lignocaine and epinephrine (1:200,000), the heart rate dropped to <30/min, which responded to an intravenous dose of atropine 0.65 mg. The rest of the perioperative period was uneventful. This subject had received bisoprolol.

Dose of isoflurane and fentanyl

The average volume percent of isoflurane delivered significantly lower in those who received bisoprolol as compared with those in the control group. The volume of liquid isoflurane used for each patient was calculated based on the average volume percent of isoflurane delivered, the fresh gas flow and the duration of anesthesia. This was also significantly lower in those patients who received bisoprolol (Table 4). The total dose of fentanyl used was significantly more (P<0.001) among those in the control group.

### Table 1: The demographic data were comparable between the two groups

| Variables               | Group A: Control (n = 15) | Group B: Bisoprolol (n = 15) | P value |
|-------------------------|--------------------------|------------------------------|---------|
| Age (years)             | 35.4±13.2                | 36±12.6                      | 0.88    |
| Male:female             | 8:7                      | 12:3                         | 0.12    |
| Body weight (kg)        | 61.9±13.8                | 61.3±10.8                    | 0.89    |
| Pre-operative hemoglobin (g/dL) | 13.04±1.01            | 13.61±0.92                   | 0.12    |

### Table 2: The estimated blood loss was significantly more in the control group. The decrease in hemoglobin was also significantly more in the control group

| Outcome variables       | Group A: Control (n = 15) | Group B: Bisoprolol (n = 15) | P value |
|-------------------------|--------------------------|------------------------------|---------|
| Duration of surgery (min) | 148±41                 | 119±16                       | 0.65    |
| Estimated blood loss (ml)  | 398.7±228.8            | 110.7±45.4                   | <0.0001 |
| Post-operative hemoglobin (g/dL) | 11.26±0.82             | 12.75±0.98                   | 0.0001  |
| Difference of pre- and post-hemoglobin (g/dL) | 1.78±0.62             | 0.86±0.28                    | <0.001  |

### Table 3: The operative field was graded by the surgeon, according to Fromme-Boezaart grading scale and it was found to be more favorable in those who received bisoprolol

| Fromme-Boezaart grades | Group A: Control (n = 15) | Group B: Bisoprolol (n = 15) | P value |
|-------------------------|--------------------------|------------------------------|---------|
| 0                       | 0                        | 0                            | −0.0001 |
| 1                       | 0                        | 8                            |         |
| 2                       | 6                        | 7                            |         |
| 3                       | 6                        | 0                            |         |
| 4                       | 3                        | 0                            |         |
| 5                       | 0                        | 0                            |         |
group (2.8 ± 0.41 μg/kg) as compared with those who received bisoprolol (1.7 ± 0.45 μg/kg).

**Discussion**

FESS is a well-accepted treatment modality for inflammatory disease of the para-nasal sinuses.[1-3] This involves passage of a high definition telescope through the nostril into the sinuses. The nasal mucosa is a very sensitive area and surgery of this region is associated with severe sympathetic stimulation causing hypertension and tachycardia. The nasal and the sinus mucosae are very vascular and bleed easily, which would severely compromise the visualization of the surgical field through the endoscope. This could result in inadvertent tissue injury leading to adhesions and scarring and even severe complications such as orbital and brain injury.[1-5] Establishing a near bloodless operative field is ideal for ease of surgery and to reduce complications.[14]

Acceptable operative conditions during FESS have been achieved with local anesthesia,[6,7] total intravenous and inhalational anesthesia.[8-10] Infiltration of the nasal mucosa with local anesthetic and epinephrine cause local vasoconstriction and reduces bleeding for a limited period of time, but this can lead to transient hypertension and tachycardia; although, depending on the sympathetic tone, profound hypotension has also been reported.[6] Topical application of cocaine (3 mg/kg) is also effective in vasoconstriction of the mucosal vasculature.[4] Steroids, administered over several pre-operative days, would reduce the inflammatory process and reduce the bleeding during surgery. Total Intravenous anesthesia with propofol, remifentanil and dexmedetomidine has been shown to reduce bleeding during FESS and provide good operating conditions.[2,15] However, the expense and the availability of these drugs could be a factor to consider.

Reducing the arterial pressure during the procedure does minimize intra-operative bleeding.[2,3,14] This is usually achieved by increasing the concentration of inhalational or intravenous anesthetic agents or inducing hypotension with the drugs such as sodium-nitroprusside. However, these techniques are associated with reflex tachycardia, which apart from being an undesirable side-effect, also increases venous oozing.[3,4] The extent of surgical bleeding depends not only on the MAP, but also on the venous pressure and the capillary blood flow. It has been suggested that decreasing the heart rate increases the diastolic time with greater filling of the venous capacitance vessels, which lowers the venous pressure over the surgical field and therefore reduces the venous oozing.[2,3]

In this study, if the initial surge due to the sympathetic stimulation of intubation and infiltration of the vasoconstrictor is ignored, the MAPs during the operative period were 70.0 ± 2.7 and 62 ± 3.6 mmHg respectively.
Beta blocker lowers the blood pressure and the heart rate and thereby reduces surgical bleeding and improves visualization. Previous studies have used single doses of metoprolol\[11\] or esmolol,\[2\] which are short acting and although did reduce the bleeding initially, the effect did not persist through the length of the surgery. As the effect of the β-blocker wore off, the heart rate and the venous tone increased leading to more bleeding.\[3\] A continuous infusion of esmolol could be used to maintain the effect, but a single, pre-operative, oral medication appears simpler to implement. This clinical trial was an attempt to study the impact of bisoprolol, a longer acting beta-blocker, in reducing the bleeding and therefore improve the operative conditions, during FESS.

The volume of blood lost during the surgery was significantly lower in those patients who received bisoprolol. This could be due to one or more of the following reasons: The negative chronotropic action of bisoprolol would reduce the frequency of pulsations of the arterioles and thus the exudation of blood per unit time from the damaged vessels; The resultant hypotension would reduce the pressure head of the blood flowing out of ruptured vessels and thus decrease the volume lost.; Bradycardia increases the diastolic period leading to lower venous pressure and thus reduce the venous oozing.

The dose of bisoprolol used was only 2.5 mg which should not cause any serious side-effects. However, one patient did have significant bradycardia and hypotension when the nasal mucosa was infiltrated with epinephrine for vasoconstriction. This could possibly be a “vaso-vagal” reflex due to stimulation of the trigeminal nucleus causing vagal stimulation and bradycardia. A low dose of epinephrine infiltrated along with the local anesthetic into the surgical field has been shown to cause transient hypotension.\[6\]

This study has also shown that bisoprolol obtunded the sympathetic response to intubation and the infiltration of the vasoconstrictor into the nasal mucosa. This would be an added advantage in patients with coronary heart disease, in whom tachycardia is undesirable. Surgery in the region of the trigeminal nerve innervation is associated with a significant sympathetic response and the resulting tachycardia and hypertension is controlled by increasing the concentration of inhalational anesthetic and aliquots of opioids. Those who received bisoprolol, needed a significantly lower dose of fentanyl and isoflurane, thereby providing both clinical and financial benefit. The volume of liquid isoflurane used in those who received bisoprolol was only 28% of that used in the control group patients. Although, there was no incidence of awareness and the percentage of isoflurane was above one minimum alveolar concentration, one of the improvements that can be added to this study is an objective measure of depth of anesthesia, such as bispectral index monitoring.

The surgical field was graded by the surgeon at the end of the surgery, providing an overall impression. While planning this study it was felt that it was important to have the surgeon’s opinion, but repeated assessment during the surgery would have distracted the surgeon, especially when the bleeding was excessive. Hence, a direct, real-time correlation between the arterial pressure or the heart rate and the Fromme-Boezaart grade of the operative field could not be performed. However, this assessment did give a global picture of the operating conditions. The decreased bleeding provided a better view for the surgeon and facilitated the speed of surgery, thereby reducing the operating time.

Therefore, this clinical trial has demonstrated that administration of a single pre-operative dose of bisoprolol (2.5 mg) can significantly reduce the blood loss during FESS and improve the visualization of the operating field and it also lowers the use of isoflurane and fentanyl needed to achieve this. The fact that the nasal mucosa is so vascular and bleeds easily definitely contributed to this low sample size study to show a significant difference (effect size) both statistically and clinically.

References

1. Tewfik MA, Wormald PJ. Ten pearls for safe endoscopic sinus surgery. Otolaryngol Clin North Am 2010;43:933-44.
2. Baker AR, Baker AB. Anaesthesia for endoscopic sinus surgery. Acta Anaesthesiol Scand 2010;54:795-803.
3. Nair S, Collins M, Hung P, Rees G, Close D, Wormald PJ. The effect of beta-blocker premedication on the surgical field during endoscopic sinus surgery. Laryngoscope 2004;114:1042-6.
4. Boezaart AP, van der Merwe J, Coetzee A. Comparison of sodium nitroprusside — And esmolol-induced controlled hypotension for functional endoscopic sinus surgery. Can J Anaesth 1995;42:373-6.
5. Albu S, Baciut M. Failures in endoscopic surgery of the maxillary sinus. Otolaryngol Head Neck Surg 2010;142:196-201.
6. Yang JJ, Li WY, Jil Q, Wang ZY, Sun J, Wang QP et al. Local anesthesia for functional endoscopic sinus surgery employing small volumes of epinephrine-containing solutions of lidocaine produces profound hypotension. Acta Anaesthesiol Scand 2005;49:1471-6.
7. Wormald PJ, Athanasiadis T, Rees G, Robinson S. An evaluation of effect of pterygopalatine fossa injection with local anesthetic and adrenalin in the control of nasal bleeding during endoscopic sinus surgery. Am J Rhinol 2005;19:288-92.
8. Wormald PJ, van Renen G, Perks J, Jones JA, Langton-Hewer CD. The effect of the total intravenous anesthesia compared with inhalational anesthesia on the surgical field during endoscopic sinus surgery. Am J Rhinol 2005;19:514-20.
9. Eberhart LH, Polz BJ, Wulf H, Geldner G. Intravenous anesthesia provides optimal surgical conditions during microscopic and endoscopic sinus surgery. Laryngoscope 2003;113:1369-73.
10. Ankichetty SP, Ponniah M, Cherian V, Thomas S, Kumar K, Jeslin L, et al. Comparison of total intravenous anesthesia using propofol and inhalational anesthesia using isoflurane for controlled
hypotension in functional endoscopic sinus surgery. J Anaesthesiol Clin Pharmacol 2011;27:328-32.
11. Gilbey P, Kukuev Y, Samet A, Talmon Y, Ivry S. The quality of the surgical field during functional endoscopic sinus surgery — The effect of the mode of ventilation — A randomized, prospective, double-blind study. Laryngoscope 2009;119:2449-53.
12. Jakobsen CJ, Grabe N, Christensen B. Metoprolol decreases the amount of halothane required to induce hypotension during general anaesthesia. Br J Anaesth 1986;58:261-6.
13. Amr YM, Amin SM. Effects of preoperative oral beta blocker versus intraoperative nitroprusside or esmolol on quality of surgical field during tympanoplasty. J Clin Anesth 2011;23:544-8.
14. Drozdowski A, Sieśkiewicz A, Siemiatkowski A. Reduction of intraoperative bleeding during functional endoscopic sinus surgery. Anestezjol Intens Ter 2011;43:45-50.
15. Goksu S, Arik H, Demiryurek S, Mumbuc S, Oner U, Demiryurek AT. Effects of dexmedetomidine infusion in patients undergoing functional endoscopic sinus surgery under local anaesthesia. Eur J Anaesthesiol 2008;25:22-8.

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