

Preoperative gabapentin versus bisoprolol for haemodynamic and surgical field optimisation during endoscopic sinus surgery: A randomised controlled trial

Address for correspondence:

Dr. Abeer M Elnakera,
Anaesthesia and Surgical
Intensive Care Department,
Faculty of Medicine,
Zagazig University, Zagazig,
Alsharqiah, Egypt.
E-mail: nakera35@hotmail.com

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**Abeer M Elnakera, Maram H Wagdy, Aymen A Abd-Elgelyl,
Mohamed W EL-Anwar¹**

Departments of Anaesthesia and Surgical Intensive Care and ¹Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine, Zagazig University, Zagazig, Alsharqiah, Egypt

ABSTRACT

Background and Aims: Appropriate premedication can optimise haemodynamics and hence surgical field visibility during endoscopic sinus surgery (ESS). This study aimed to compare the intraoperative effect of gabapentin 1200 mg versus bisoprolol 2.5 mg, given 2 hours before ESS.

Methods: Patients were assigned into one of three groups. Patients of gabapentin group received preoperative oral gabapentin 1200 mg while, patients of bisoprolol and control groups received oral bisoprolol 2.5 mg and placebo respectively 2 hours before ESS. Primary outcome: reduction of blood loss and surgical field quality. Secondary outcome: haemodynamic control. mean arterial pressure (MAP) and heart rate (HR) were recorded as baseline, before and after induction of anaesthesia, at 1, 5, 10, 15 minutes after intubation and then every 15 minutes until the end of surgery. Data also included Fromm and Boezaart category scale (assessed every 15 min), intraoperative blood loss, surgeon satisfaction score, intraoperative anaesthetic/analgesic and vasoactive medications requirements. **Results:** Out of 66 eligible patients, 60 patients completed the study. Intraoperative MAP and HR were significantly lower and more stable in gabapentin and bisoprolol groups compared to control group ($p < 0.05$). The volume of blood loss was significantly lower ($p 0.000$) and operative field was more visible in gabapentin and bisoprolol groups than those in control group ($p 0.000$). **Conclusion:** The beneficial effect of gabapentin 1200 mg on intraoperative haemodynamic control and surgical field visibility is comparable to that of bisoprolol 2.5 mg when either of them is given as a single oral dose 2 hours before ESS.

Key words: Bisoprolol, gabapentin, haemodynamic, surgical field

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INTRODUCTION

Endoscopic sinus surgery (ESS) represents one of the most performed surgical otorhinolaryngology procedures that require good surgical field visibility.^[1] Haemodynamic optimisation through heart rate (HR) control, during general anaesthesia (GA) for ESS, has been believed to be superior to reduction of systemic vascular resistance and hypotension with respect to the surgical field quality.^[2] Appropriate oral premedication can provide a smooth approach to optimise the intraoperative haemodynamics without compromising patient safety.^[3] Oral propranolol and metoprolol have shown to be effective in providing bloodless surgical field during ESS, but their short

duration of action limits their efficacy.^[4] Bisoprolol is a longer acting β_1 antagonist that can cover this limitation.^[5] Gabapentin, a structural analogue of GABA, is a multimodal drug that can represent an interesting

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alternative to optimise haemodynamics during ESS.^[6] Only few studies have investigated the effect of bisoprolol or gabapentin premedication on intraoperative surgical field quality and haemodynamics during ESS.^[5,6]

This study aimed to compare the intraoperative effect of oral gabapentin 1200 mg versus oral bisoprolol 2.5 mg, given 2 hours before ESS on haemodynamics and surgical field visibility.

METHODS

This prospective randomised double-blinded controlled study was carried out in anaesthesia and otorhinologic surgery departments of our university hospital during the period between September 2015 to December 2016 after obtaining Institutional Review Board (IRB) approval (N. ZU-IRB 2139-24-5-2015) and patients' written informed consent. The study was registered on Clinical trial Gov. PRS. Registry name: NCT03850093 URL: <https://clinicaltrials.gov/ct2/show/NCT03850093>. This manuscript adheres to the applicable CONSORT guidelines.

Inclusion criteria were American Society of Anesthesiologists (ASA) class I or II, age 18- 50 years and scheduled for functional ESS. Exclusion criteria were suspected difficult airway, basal HR <60/min., chronic cardiovascular or cerebrovascular diseases, bronchial asthma or chronic obstructive pulmonary disease, diabetes mellitus, bleeding disorders, anaemia, renal or hepatic insufficiency, psychiatric disorders, chronic treatment by β -blockers (β Bs), gabapentin or drugs that affect coagulation, and/or contraindications to any of the study drugs.

Eligible patients were randomised according to random list generated software and allocated (closed envelope technique) to one of 3 groups: gabapentin group (group G), bisoprolol group (group B) and control group (group C). All patients received the assigned study drug with sips of water, 2 hours before induction of anaesthesia. Patients of group G were premedicated with oral gabapentin 1200 mg (Conventin 400 mg; Evapharm) while, patients of group B were premedicated with oral bisoprolol 2.5 mg (Concor 2.5 mg; Merck/Amoun) and patients of group C were premedicated with oral vitamin C 1000 mg (C retard 500 mg; Hikma Pharma S.A.E) as placebo. The primary outcome was the volume of blood loss and surgical field quality. The secondary outcome was haemodynamic control.

The same anaesthetist and surgeon, who were blinded to the used premedication, managed all planned ESS procedures. The surgeon was blinded to the monitor recording the haemodynamic variables. All patients had been preoperatively evaluated and prepared. Patient was premedicated with intravenous (IV) atropine 20 μ g/kg immediately before admission to the operating room.

On admission to the operating room, standard monitoring was applied (B40i Monitor - GE Healthcare, Finland). Anaesthesia was induced with IV propofol 2 mg/kg and fentanyl 1 μ g/kg. Cisatracurium 0.15 mg/kg IV was given to facilitate laryngoscopy and intubation (LI). The patient was ventilated using tidal volume 6-8 mL/kg and respiratory rate that achieved an end-tidal carbondioxide (EtCO₂) of 30-35 mmHg. Oropharyngeal pack was inserted. Anaesthesia was maintained with isoflurane based on minimum alveolar concentration (MAC) 1.2% until a steady state of anaesthesia was achieved (defined as a state of anaesthesia when no changes in haemodynamic variables take place for at least 10 min). An increase of $\geq 20\%$ of basal value in both HR and mean arterial pressure (MAP) was treated with increasing the concentration of isoflurane by 0.5% and increments of fentanyl 1 μ g/kg. Cisatracurium 0.03 mg/kg was given every 20 min. IV lactated ringer solution was infused at 6 ml/kg/hour. All patients were positioned supine and the bedhead of the surgical table was raised by 30° to improve venous drainage. Before the beginning of surgical procedure, well wrung out cotton pledgets soaked with 4 ml of 2% lignocaine with 1:200,000 adrenaline were topically applied to the nasal mucous membrane for 10 min (no infiltration). Target MAP was 60-70 mmHg during the surgical procedure to achieve Fromm and Boezaart category scale of 2 or 3 which is judged to be optimal for surgery.^[7] If the MAP was still >70 mmHg in spite of increasing isoflurane inhalation to 2.5%, IV fentanyl 50 μ g was administered followed by nitroglycerine (1-10 μ g/kg/min) infusion titrated to effect. If the HR was more than 100 beats per minute (bpm), IV propranolol was titrated 1-3 mg/hour to reduce HR to <90 bpm. If MAP decreased to <60 mm Hg, IV ephedrine 3 mg increments were given. If HR decreased to <60 bpm, IV atropine in 0.5 mg increments was given. 15 minutes before ending surgery, the infusion of any vasoactive medication was stopped and the anaesthetic agent was decreased allowing haemodynamics to return to their basal value. On completion of surgical procedure, anaesthesia was discontinued and reversal

of neuromuscular blockade was achieved using IV neostigmine 0.08 mg/kg and atropine 20 µg/kg. On the start of obeying commands, patients were extubated and shifted to recovery room. Patients were discharged to the ward after reaching a score ≥ 9 on the Modified Aldrete score. During postoperative period up to 6 hours, patients were monitored to detect and address any postoperative complications.

Collected data were patients' age, gender, body weight, indication and side of ESS, surgical time (starting from the application of local anaesthetic to the end of surgery), haemodynamics (HR and MAP) that were recorded before oral premedication (baseline), pre-induction, after induction of anaesthesia, 1, 5, 10, 15 min after intubation and then every 15 minutes until the end of surgery, the highest intraoperative isoflurane percentage, the need for additional intraoperative fentanyl administration (other than that given during induction of anaesthesia), the need for additional IV intraoperative vasodilators or β Bs, intraoperative blood loss calculated by adding blood volume in the suction bottle to that derived from 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),^[8] the quality of the operative field (Fromm and Boezaart category scale) [Annexure 1] assessed by the surgeon every 15 minutes from the start of surgical procedure,^[9] surgeon satisfaction scale at the end of surgery (where given 5 for very satisfied, 4 for satisfied, 3 for neutral, 2 for dissatisfied and 1 for very dissatisfied), patients' agitation on admission to recovery room based on the Richmond Agitation Sedation Scale (RASS)) [Annexure 2],^[10] recovery time (starting from endotracheal extubation to Aldrete score ≥ 9), intraoperative and postoperative (up to 6 hours) complications in the form of hypertension (defined as MAP elevation by $>20\%$ of base line value), hypotension (defined as SAP <90 mmHg or MAP <60 mmHg), tachycardia (defined as HR ≥ 100 BPM), bradycardia (defined as HR ≤ 60 BPM) or episodes of postoperative nausea and vomiting (PONV).

With 80% power of the study, 95% confidence interval (CI) and calculated volume of blood loss 200 ± 40 ml and 150 ± 55 ml on gabapentin^[11] and bisoprolol^[5] premedication respectively, the estimated sample size was 54 patients (open EPI). 63 patients were included in the study to compensate for drop out.

Continuous parametric data were presented as mean and standard deviation (SD) and compared using one-way

analysis of variance (ANOVA)(F) followed by post-hoc analysis for intergroup comparison. Repeated measures of ANOVA was used for intragroup comparison. Non-parametric data were presented as median and range and compared using Kruskal Wallis test. Qualitative data were presented as number (percentage) and compared using Chi-square test (X^2). P value <0.05 was considered significant. Statistical analysis was performed in Statistical Package for the Social Sciences(SPSS) version 24.

RESULTS

Out of 66 eligible patients, 3 patients were excluded (2 of them were asthmatic and the last for hypertension). 63 patients were enrolled, 22 patients were allocated to either group G or group B and the last 19 patients were allocated to group C. 1 patient and 2 patients were withdrawn from group G and C respectively due to cancellation of surgery. 60 patients completed the study [Figure 1]. There were non-significant differences among all studied groups regarding patient characteristics, surgical time, indication and side of ESS ($p > 0.05$) [Table 1].

The average basal MAP was significantly higher in groups G and B when compared to control group ($p 0.019$) with no significant difference between bisoprolol and gabapentin groups. Average MAP was significantly lower in patients of group G and B compared to control group before induction of anaesthesia, 1, 5, 10, 15, 60 and 75 minutes after endotracheal intubation with no significant difference between bisoprolol and gabapentin groups. The average MAP was comparable among the studied groups at the remaining measuring points [Figure 2].

Average baseline HR was significantly higher in gabapentin group compared to other groups ($p 0.04$). All heart rate values were significantly lower in group G and B when compared to control group, with no significant difference recorded between bisoprolol and gabapentin groups at all the measuring points [Figure 3].

Hemodynamic swings were more evident between patients of control group compared to other groups. No intraoperative IV vasoactive medications were needed for patients of group G and B but they were administered to 6 patients of control group [Table 2].

The volume of sucked blood was significantly lower in groups G and B compared to group C

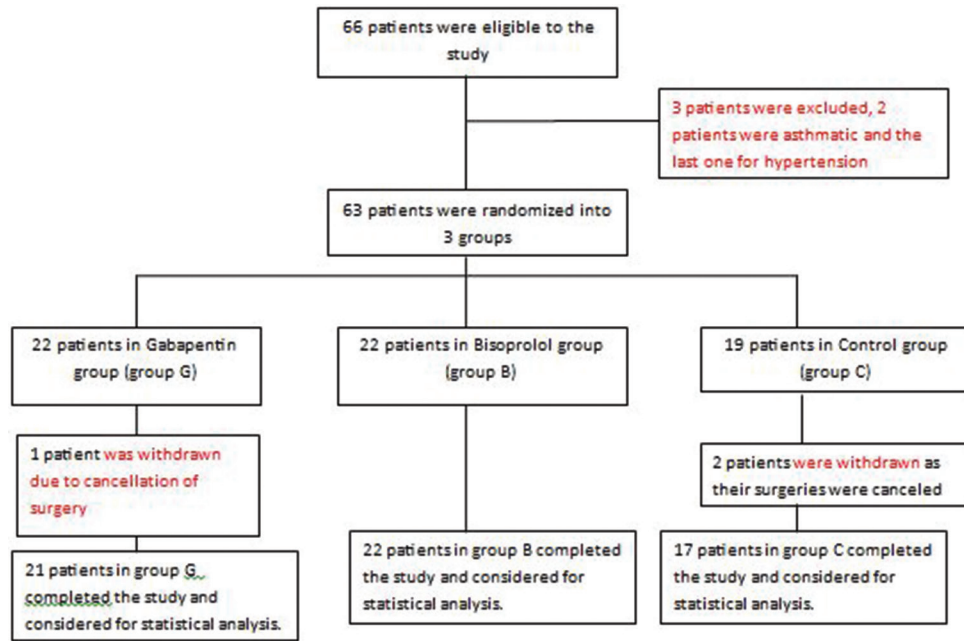


Figure 1: COSORT flow chart

Table 1: Demographic characteristics, surgical time, indications, and side of nasal surgery								
	G (n=21)		B (n=22)		C (n=17)		FIKW	P
Age (years)*	27.1±7.6		30.5±6.6		28.6±5.1		1.4	0.24
Weight (kg)*	87.1±1.1		87.9±11.9		84.5±11.5		0.44	0.64
Surgical time (minutes)†	90 (30-110)		75 (30-110)		90 (45-120)		1.17	0.56
	n	Proportion	n	Proportion	n	Proportion	X ²	
Gender								
Male	13	13/21	13	13/22	11	11/17	0.13	0.93
Female	8	8/21	9	9/22	6	6/17		
Indication of ESS								
Polyp	11	11/21	13	13/22	10	10/17	0.242	0.896
Sinusitis	10	10/21	9	9/22	7	7/17		
Side of ESS								
Bilateral	14	14/21	11	11/22	9	9/17	1.349	0.509
Unilateral	7	7/21	11	11/22	8	8/17		

Data were presented as number and proportion, compared using Chi-square test (X²). *Data were presented as mean and SD, compared using one-way ANOVA (F). †Data were presented as median and range, compared using Kruskal Wallis test (KW). No significant difference was found between all groups (P>0.05). ESS=Endoscopic sinus surgery

(p 0.000) with no significant difference between gabapentin and bisoprolol groups (p 0.464). Surgeon satisfaction (surgeon satisfaction score ≥4) was achieved for all patients of groups G and B compared to only 7 patients in control group (p 0.000) [Table 2]. Fromm and Boezaart category scale, was also significantly better in groups G and B patients than in control group (p < 0.05) with no difference between groups G and B (p > 0.05) [Figure 4].

The highest inhaled isoflurane concentration showed no difference between all groups (p 0.07). However, no intraoperative supplemental fentanyl was needed for patients of groups G and B while fentanyl was administered to 11 patients of group C (p 0.000).

Patients of B and G groups showed significantly shorter recovery time compared to control group (p 0.000 and 0.031 respectively) with no significant difference between treatment groups (p 0.230). On recovery, RASS values differed between all groups (Annexure 3). No patient of group G or B suffered agitation on recovery from general anaesthesia while 5 patients of group C were agitated during recovery (p 0.001).

For all patients, no haemodynamic instability or surgical complications were recorded during postoperative period. The proportions of patients who suffered postoperative nausea were significantly lower in group G and B (0 and 3/22 respectively) compared to that in control group (5/17) (p 0.019). Only one patient

Table 2: Intraoperative volume of blood loss, surgeon satisfaction, vasoactive medications, and incidence of haemodynamic swings

	G (n=21)		B (n=22)		C (n=17)		KW	P
Volume of Blood loss (ml)*	20 (10-40)		20 (10-30)		80 (30-110)†		17.7	0.000
	n	proportion	n	proportion	n	proportion	Fisher exact	
Frequency of procedure's Achievement of surgeon satisfaction (surgeon satisfaction score ≥4)	21	21/21	22	22/22	7	7/17‡	25.739	0.000
Patients who needed IV nitroglycerine	0	0	0	0	5	5/17†	10.145	0.001
Patients who needed IV propranolol	0	0	0	0	1	1/17	2.271	0.275
Patients who needed IV nitroglycerine and propranolol combination	0	0	0	0	6	6/17†	12.918	0.000
Patients who developed episodes of								
Hypertension	0	0	0	0	10	10/17†	26.411	0.000
Hypotension	0	0	1	1/22	7	7/17†	16.198	0.000
Tachycardia	0	0	0	0	9	9/17†	27.726	0.000
Bradycardia	0	0	4	4/22	4	4/17	5.56	0.062

Data were presented as number and proportion, compared using Fisher exact test. *Data were presented as median and range, compared using Kruskal Wallis test (KW). †Significantly higher compared to gabapentin and bisoprolol groups (P<0.05). ‡Significantly lower than that of gabapentin and bisoprolol groups (P<0.05)

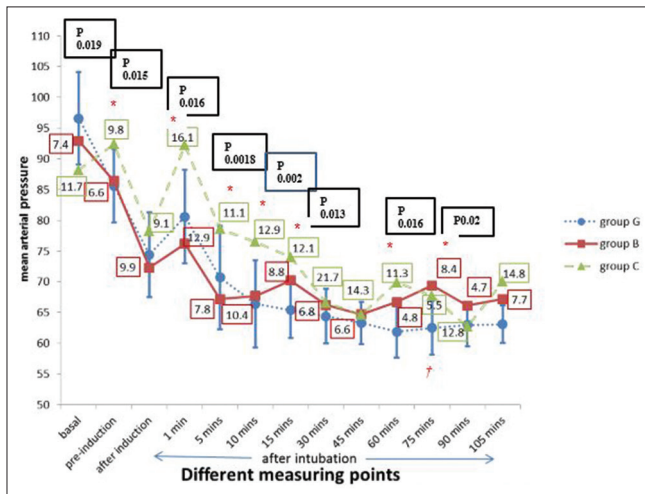


Figure 2: Intraoperative changes in mean arterial pressure [MAP (mmHg)] among the studied groups

in group C suffered postoperative vomiting (controlled by metoclopramide).

DISCUSSION

The current study showed that oral premedication with gabapentin is comparable to that of bisoprolol in improving surgical field quality, surgeon satisfaction and optimising haemodynamics during ESS. Their use is also associated with shorter recovery time and less agitation on recovery.

HR reduction is believed to be superior to decreasing SVR with respect to the surgical field quality during ESS.^[2,12] A significant correlation has been recorded between surgical scores and HR, but not MAP, on premedication with oral metoprolol.^[13] A continuous infusion of esmolol can maintain the effect, but a single, pre-operative, oral medication appears easier to implement.^[5,8]

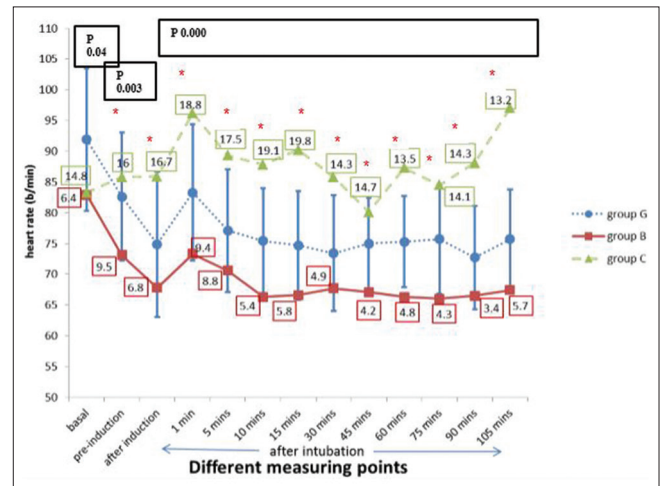


Figure 3: Intraoperative changes in heart rate [HR (b/min)] among the studied groups

Being selective β_1 B and having longer duration of action, oral bisoprolol can represent an effective choice for improving surgical field visibility.^[5] Gabapentin also can represent a better alternative to BBs due to its anxiolytic, analgesic and antiemetic potential roles as well as its ability to attenuate haemodynamic response to intense sympathetic stimulation and to prevent postoperative delirium.^[14-16]

Haemodynamic optimisation is thought to start from attenuation of stress response to laryngoscopy and intubation (LI). In agreement to the current study, significant attenuation of sympathetic response to LI and nasal mucosal infiltration by local anaesthetic and epinephrine, has been reported in some studies on premedication with either oral bisoprolol 2.5 mg, 90 minutes before surgery or different doses of gabapentin (400, 800 and 1200 mg), 1-2 hours before surgery.^[5,8,17,18] In contrast, other studies could not

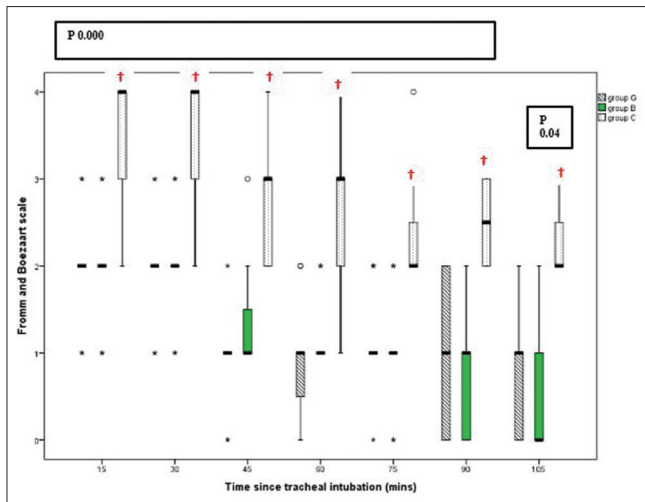


Figure 4: Quality of operative field (Fromm and Boezaart category) among the studied groups

demonstrate attenuation of tachycardic response to LI on pre-treatment with oral gabapentin either as 1600 mg in 4 divided doses on the day before surgery, or as 800-900 mg 2 hours before surgery.^[6,7,19,20] The difference in results may be explained by different dosage or regimen of administration. The effect of gabapentin dosage variations has been shown in Bafna *et al.* study^[21] in which, preoperative gabapentin 1000 mg, but not 600 mg, could attenuate haemodynamic response to LI.

In accordance with our study findings, a reduction of intraoperative requirements of sodium nitroprusside infusion has been reported in patients who received oral gabapentin 1200 mg 1 h before endoscopic nasal surgery.^[11]

In contrast to the current findings, Farzi and associates could not demonstrate any difference between patients who received gabapentin 900 mg, 2 hours before surgery, and those who did not as regards the amount of bleeding during septorhinoplasty and the difference may be due to this difference in the used gabapentin dose.^[6] Similar to current study, previous studies showed a reduction of blood loss and a better visualisation of the operating field during ESS on bisoprolol (2.5 mg) premedication.^[5,16]

Jacob and associates reported a reduction of both inhaled isoflurane and IV fentanyl requirements during ESS without any increase in the incidence of awareness on pre-treating patients with bisoprolol 2.5 mg.^[8] Salama and Amer have also revealed a reduction in both intraoperative remifentanyl and sevoflurane administration on pre-treating patients with gabapentin 1200 mg.^[22] The difference between

our study results which showed no difference in inhaled isoflurane concentration, and those of Jacob *et al.* study and Salama and Amer study may be attributed to the use of bispectral index (BIS) to guide anaesthetic administration in both studies.

Shorter recovery time in bisoprolol or gabapentin groups may be due to lower opioid administration for those groups of patients in the current study.^[23,24]

In a similar study, Jacob *et al.* reported that one patient developed bradycardia and hypotension on using bisoprolol in a similar dosage;^[8] on the other hand, Sophia *et al.* reported no side effects related to bisoprolol administration.^[5]

One of our study limitations is that BIS monitoring was not available to us. Another limitation is that baseline MAP and/or HR values were higher in the treatment groups compared to the control group. However, this finding may support the beneficial effect of gabapentin and bisoprolol on intraoperative haemodynamic control.

CONCLUSION

The current study proved that the beneficial effect of gabapentin 1200 mg on intraoperative haemodynamic control and surgical field visibility is comparable to that of bisoprolol 2.5 mg when either of them is given as a single oral dose 2 hours before ESS.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTAL MATERIALS

Annexure 1: Quality of surgical field (Fromm and Boezaart category scale)^[7]

Score=

0	No Bleeding.
1	Slight bleeding- no blood suctioning required.
2	Slight bleeding- occasional blood suctioning required.
3	Slight bleeding- frequent blood suctioning required, operative field is visible for some seconds after evacuation
4	Moderate bleeding- frequent blood suctioning required; operative field is only visible immediately after evacuation
5	Severe bleeding-constant blood suctioning required; bleeding appears faster than can be removed by suction. Surgery is hardly possible, and sometimes impossible

Annexure 2: Patients' agitation on admission to recovery room based on the Richmond Agitation Sedation Scale (RASS)^[10]

Scale	Label	Description
+4	COMBATIVE	Combative, violent, immediate danger to staff
+3	VERY AGITATED	Pulls to remove tubes or catheters; aggressive
+2	AGITATED	Frequent non-purposeful movement, fights ventilator
+1	RESTLESS	Anxious, apprehensive, movements not aggressive
0	ALERT & CALM	Spontaneously pays attention to caregiver
-1	DROWSY	Not fully alert, but has sustained awakening to voice (eye opening & contact >10 sec)
-2	LIGHT SEDATION	Briefly awakens to voice (eyes open & contact <10 sec)
-3	MODERATE SEDATION	Movement or eye opening to voice (no eye contact)
-4	DEEP SEDATION	No response to voice, but movement or eye opening to physical stimulation "Touch".
-5	UNAROUSABLE	No response to voice or physical stimulation "Touch".

Annexure 3: Intraoperative highest percentage of isoflurane, need for additional fentanyl, recovery time and Richmond Agitation Sedation Scale (RASS)

	G (n=21)		B (n=22)		C (n=17)		KW Fisher exact	P
	n	Proportion	n	Proportion	n	Proportion		
Patients who needed additional IV fentanyl*	0	0	0	0	11	11/17 [†]	30.525	0.000
Highest concentration of inhaled isoflurane (%)	2	(1.5-2.5)	2	(1.5-2.5)	2	(1.8-3)	5.17	0.075
Recovery time (min)	15	(5-20)	10	(6-15)	15	(10-20) [†]	17.7	0.000
RASS	0	(-1-1) [‡]	0.5	(0-1)	1	(1-2) [†]	33.2	0.000

Data were presented as median and range, compared using Kruskal Wallis test (KW). *Data were presented as number and proportion, compared using Fisher exact test. [†]Significantly higher compared to both gabapentin and bisoprolol groups (P<0.05). [‡]Significantly lower than that of bisoprolol group (P<0.05)