Comparison of surgical conditions following premedication with oral clonidine versus oral diazepam for endoscopic sinus surgery: A randomized, double-blinded study

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Abstract

Background and Aims: Endoscopic sinus surgery (ESS) provides a challenge and an opportunity to the anesthesiologists to prove their mettle and give the surgeons a surgical field which can make their delicate surgery safer,more precise and faster. The aim of the study was to evaluate the surgical field and the rate of blood loss in patients premedicated with oral clonidine versus oral diazepam for endoscopic sinus surgery.

Material and Methods: ASA I or II patients who were scheduled to undergo ESS were randomly allocated to group D ($n = 30$) or group C ($n = 30$). The patients' vital parameters, propofol infusion rate, and rate of blood loss were observed and calculated. The surgeon, who was blinded, rated the visibility of the surgical field from grade 0-5.

Results: In the clonidine group, the rate of blood loss, the surgical time, propofol infusion rate was found to be statistically lower as compared to the diazepam group. Also a higher number of patients in the clonidine group had a better surgical score (better surgical field) than the diazepam group and *vice versa*.

Conclusions: Premedication with clonidine as compared to diazepam, provides a better surgical field with less blood loss in patients undergoing ESS.

Key words: Anesthesia, blood loss, clonidine, endoscopic sinus surgery, intravenous propofol, premedication, surgical field

Introduction

Surgical bleeding during functional endoscopic sinus surgery (FESS) decreases the visibility of the surgical field during an intervention, increases the incidence of serious vascular, orbital, and intracranial complications, prolongs surgical duration, and reduces the quality of intervention.

Various methods such as preoperative adrenaline packing of the nasal cavity, intraoperative adrenaline infiltration of nasal mucosa, patient head elevation and/or hypotensive anesthesia, have been adopted to provide an optimal field.[1]

Clonidine being a centrally acting α_2 agonist, when used as a premedicant, is known to enhance the hypotensive effects of inhalation agents without the disadvantages of intravenous vasodilators.[2] It was found that when oral clonidine was given as premedication, it provided a clear surgical field and reduced the bleeding during endoscopic sinus surgery under general anesthesia with halothane.[2] Studies have also shown that propofol anesthesia results in a similar or a better

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surgical field and lesser amount of bleeding than sevoflurane or isoflurane anesthesia.[1] We aimed to provide an optimal field and evaluate if using premedication with oral clonidine in propofol anesthesia provided a better field as compared to oral diazepam.

Material and Methods

The study was conducted over a period of 18 months. Patients of 18-45 years of age, of either sex, weighing 40-70 kg, belonging to American Society of Anesthesiologists I or II, and scheduled for FESS were recruited. Patients on treatment with drugs known to affect the heart rate, blood pressure, patients with baseline heart rate <60 beats/min, patients with a bleeding diathesis, and those on anticoagulants were excluded from the study.

Since a study of rate of blood loss ml/hour was planned, a continuous response variable from independent groups of clonidine and diazepam subjects with 1 subject per each group was selected. In a previous study, the response within each subject group was normally distributed with standard deviation (SD) at 16 ml blood loss. If the true difference in mean blood loss in the clonidine and diazepam is 15 ml (effect size = 0.967), we will need to study 29 clonidine subjects and 29 diazepam subjects to be able to reject the null hypothesis that the population mean blood loss of the clonidine and diazepam groups are equal with probability (power) of 0.8. The type I error probability associated with this test of this null hypothesis is 0.05.

Thus, 30 subjects were selected to receive oral clonidine and 30 subjects were selected for oral diazepam group. The sample size was estimated using G*Power 3.1.6 software (Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behavior Research Methods 2009; 41:1149-1160).. A written, informed consent was obtained from each patient, and the study was approved by our Institution's Ethics Committee.

The extent of the lesion was determined preoperatively and was classified as high (>12) and low (≤12) Lund-Mackay (LM) scores according to the computed tomography (CT) findings.[1]

This study was designed in a randomized, double-blinded fashion and the patients were divided into two groups according to the premedication they received.

Group C (*n* = 30) – received tablet clonidine 4 μg/kg (maximum 200 μg)

Group D (*n* = 30) – received tablet diazepam 0.2 mg/kg (maximum 10 mg)

All the patients were given the premedication, in the preoperative room, 90-120 min prior to surgery, and an assessment was done just prior to the premedication and 90 min later.

The randomization was done using a table of random numbers and the anesthesiologist recording the findings and the operating surgeon were blinded to the premedicant drug.

The heart rate, blood pressure, and arterial blood saturation were recorded preoperatively by the blinded anesthesiologist using a noninvasive monitor.

The patients were monitored with electrocardiogram, noninvasive blood pressure monitor, and pulse oximetry. After preoxygenation with 100% oxygen, anesthesia was induced with intravenous propofol 2-2.5 mg/kg, fentanyl 2-2.5 μg/kg, and muscle relaxation was achieved with vecuronium 0.1 mg/kg. After tracheal intubation, lungs were ventilated with a mixture of oxygen and nitrous oxide. Anesthesia was maintained with a decremental infusion of propofol at 10 mg/kg/h for 10 min followed by 6 mg/kg/h until the termination of procedure. Fentanyl top-up of 1 μg/kg was administered every hourly. The target mean arterial pressure (MAP) was maintained between 70 and 80 mmHg and the heart rate within 60-70 beats/min. To achieve this, wherever necessary, an additional dose of 1 μg/kg of fentanyl was given and/or adjustment in the propofol infusion rate was made up to a maximum of 150 μg/kg/min.

Intra-operative bradycardia was defined as heart rate <20% of baseline or absolute heart rate <40 beats/min, in which case intravenous atropine 0.6 mg was administered.

Similarly, a fall in mean blood pressure, below 60 mmHg was treated with ephedrine, 6 mg bolus. An increase in the heart rate or MAP was managed with intravenous metoprolol. When any other additional measures were required to maintain the parameters within the required limits, the case was excluded. If the surgical time extended beyond 3 h, then the case was excluded. The end-tidal CO_2 was continuously monitored and adjusted to the target concentration of 30-40 mmHg by controlling minute ventilation with tidal volume ranging from 8 to 10 ml/kg and respiratory rate from 10 to 16 cycle/min. Patients were positioned in the 20° reverse Trendelenburg position and 1:2,00.000 epinephrine was infiltrated in the nasal mucosa by the operating surgeon. Patients were infused with a crystalloid solution of 4 ml/kg. The fluid replacement subsequently was according to the standard requirement

according to the body weight using crystalloids and blood replacement was using ringer lactate solution in the ratio of 3:1. After completion of surgery, neuromuscular blockade was antagonized; patients were extubated and shifted to the recovery room. Intraoperative bleeding was assessed by the blinded surgeon according to the scoring scale proposed by Boezaart *et al.*[3]

0 = No bleeding.
1 = Slight bleeding; no suctioning required.
2 = Slight bleeding; occasional suctioning required.
3 = Slight bleeding; frequent suctioning required. Bleeding threatened the surgical field a few seconds after suction was removed.
4 = Moderate bleeding; frequent suctioning required. Bleeding threatened surgical field directly after suction was removed.
5 = Severe bleeding; surgery not possible.

Measurement of blood loss

Five milliliter of 1:250,000 heparin was given to the scrubbed nurse at the start of the surgery and the fluid was suctioned into the suction bottle to be used for the surgery. At the end of surgery, the amount of intraoperative blood loss was calculated from the patient's hemoglobin (Hb) and the amount of blood in the suction canister using the equation:

Blood loss (ml) = Hb (g/dl) × V (ml)/Hbm (g/dl).
V = Fluid volume in the suction canister.
Hb = Hemoglobin concentration in the suction canister.
Hbm = Patient's mean hemoglobin concentration (mean Hb at the beginning and at the end of surgery).

The rate of blood loss was then calculated by dividing the blood loss obtained in each case with the duration of surgery and expressed as rate of blood loss = ---ml/h.

Statistical tests done

Data were expressed as mean ± SD or as absolute values. Data such as surgical field, Lund-Mackay-CT (LM-CT) score; use of atropine, fentanyl, and beta-blocker were compared using the Chi-square test. Blood loss was compared using

the Student's *t*-test. The Student's *t*-test was used to compare prospective, repeated measures. The level of significance was set at $P < 0.05$.

Results

There were no significant differences in the mean age, sex, weight, preoperative MAP, and heart rate, between the two groups as shown in Table 1. Furthermore, the patients with LM-CT score of ≤12 and >12 were found to be evenly distributed between the two groups with the difference not being statistically significant.

The difference in the heart rate between the two groups was not statistically significant ($P < 0.05$) in the preoperative period and 1-min and 5-min after laryngoscopy [Table 2]. The increase in the heart rate following adrenaline infiltration was not significant either ($P > 0.05$) between the two groups. From 15 min after the start of surgery until the end of surgery, the heart rate was better maintained in the clonidine group. The difference in the heart rate from 15 min to 2 h 30 min between the two groups was statistically significant. The difference was not found to be statistically significant during extubation or in the recovery period.

Comparison of MAP between the two groups (mmHg) at different time intervals is shown in Table 3. The target mean blood pressure was achieved with more ease and better maintained in the clonidine group. The difference in the MAP between the two groups, though not significant in the preoperative period, was statistically significant following 1-min, 5-min following laryngoscopy, following adrenaline infiltration, and throughout the surgical period including the extubation period and recovery.

The rate of bleeding was less in the clonidine group and the difference was found to be statistically significant ($P < 0.05$). A significantly longer time was required to complete the surgery in the diazepam group, 136 min (mean surgical time) as compared to 111 min clonidine group. Although the number of patients who required an additional dose of fentanyl was found to be higher in the diazepam group as compared to the clonidine group, this difference was not found to be statistically significant

Table 1: Patient characteristics

Group	Age (years)	Weight (kg)	Sex (male/female)	LM-CT score (%)		Heart rate (beats/min) Before induction	MAP (mmHg), before premedication
				≤12	>12		
Diazepam Group D (*n*=30)	31.17	54.47	21/9	26 (86.7)	4 (13.3)	85.9	90.8
Clonidine Group C (*n*=30)	30.20	56.23	23/7	27 (90)	3 (10)	79.5	89.0
P	0.61	0.30		075	0.688	0.1	0.63

P < 0.05 is considered as statistically significant. There is no statistically significant difference in the above-mentioned parameters between the two groups,
LM-CT = Lund-Mackay-computed tomography, MAP = Mean arterial pressure

Table 2: Comparison of the mean heart rate between the two groups

Group	Preoperative	Ln1	Ln5	Adrenaline infiltration	15 min	30 min	45 min	1 h	1.15	1.30	1.45	2 h	2.15	2.30	2.45	3 h	Extubation	Recovery
Group D																		
Mean	79.40	85.97	79.33	86.80	77.17	74.60	71.60	73.30	72.83	72.71	73.40	73.50	73.44	72	76.50	75.60	85	75.20
SD	17.39	16.69	15.36	13.94	13.67	13.92	11.70	11.84	10.81	12.02	11.24	12.33	11.86	14.30	14.19	14.72	16.47	19.41
Group C																		
Mean	79.97	78.97	73.73	83.37	70.87	67.93	64.62	65.64	66.41	67.32	65.64	66.12	66	64.40	66.38	67.25	79.13	68.13
SD	22.61	15.88	12.94	14.08	12.01	11.52	11.92	8.42	10.24	9.52	8.84	8.80	10.78	11.58	13.60	13.50	11.99	13.54
P	0.914	0.102	0.132	0.347	0.063	0.048	0.027	0.007	0.006	0.037	0.091	0.012	0.044	0.085	0.192	0.229	0.107	0.115

The mean heart rate between the two groups differed significantly from 15 min after the start of surgery to 2 h 30 min, with the mean heart rate in the clonidine group being lower than the diazepam group. Statistical test used: Student's t-test, SD = Standard deviation, Ln = laryngoscopy, Ln1 = 1 minute after laryngoscopy, Ln5 = 5 minutes after laryngoscopy

Table 3: Comparison of MAP between the two groups (mmHg)

Group	Preoperative	Ln1	Ln5	Adrenaline infiltration	15 min	30 min	45 min	1 h	1.15	1.30	1.45	2 h	2.15	2.30	2.45	3 h	Extubation	Recovery
Group D																		
Mean	89.87	94.83	82.20	90.57	78.27	77.87	76.90	78.97	78.62	79.75	81.08	80.90	84.13	85	84.11	83.33	96.78	86.11
SD	13.9	13.40	10.49	14.20	11.41	10.19	9.24	10.83	9.90	10.14	11.12	9.76	8.45	9.95	10.79	10.23	8.85	14.53
Group C																		
Mean	88.03	81.43	75.83	79.13	71.37	71.13	69.03	71.39	69.45	70.05	71.41	71.53	72.59	72.75	73.25	73.38	89.25	75.88
SD	11.44	11.92	10.57	16.09	10.18	10.74	9.98	9.29	5.44	5.34	5.01	4.82	7.25	5.54	5.80	5.878	10.67	8.25
P	0.579	0.000	0.023	0.005	0.016	0.016	0.003	0.006	0.000	0.000	0.000	0.001	0.000	0.01	0.021	0.024	0.000	0.005

The difference between the two groups, though not significant preoperatively was found to be statistically significant throughout the intra-operative period (P < 0.05). Statistical test used: Student's t-test. SD=Standard deviation, MAP = Mean arterial pressure, Ln = laryngoscopy, Ln1 = 1 minute after laryngoscopy, Ln5 = 5 minutes after laryngoscopy

Table 4: Mean propofol infusion rate and the rate of blood loss was statistically significant (*P*<0.05)

Group	Number of patients (%)			Mean propofol infusion rate (mcg/kg/min)	Rate of blood loss (ml/h)	Surgical time (min)
	Use of beta-blocker	Use of atropine	Additional fentanyl use			
Diazepam (*n*=30)	5 (16.7)	0 (0)	7 (23.3)	127.83	37.7 (SD=18.71)	136
Clonidine (*n*=30)	0 (0)	2 (6.66)	3 (10)	116.66	20 (SD=13.97)	111
P	0.052	0.492	0.149	0.027	0.001	0.016

Also, the use of beta-blocker in the diazepam group was significantly higher. Atropine use and additional fentanyl use was not significantly different between the two groups. A significantly longer time was required for completion of surgery in the diazepam group (P < 0.05). Statistical tests used: Rate of blood loss - Student's t-test; Others - Chi-square test. SD=Standard deviation

Table 5: Comparison of the surgical grades between the two groups

Surgical grades	0	1 (%)	2 (%)	3 (%)	4 (%)	5
Diazepam (*n*=30)	0	2 (6.7)	18 (60)	6 (20)	4 (13.3)	0
Clonidine (*n*=30)	0	6 (20)	23 (76.7)	1 (3.3)	0 (0)	0

Difference was statistically significant (P < 0.05). Statistical test used: Chi-square test

(*P* > 0.05). Two cases in the clonidine group developed a heart rate of 40/min, 42/min, and 45/min after the start of surgery, which had to be treated with intravenous atropine. None of the patients in the diazepam group needed atropine. This difference however was not statistically significant. Five patients in the diazepam group needed a beta-blocker, 3 of them, 45 min and 2 patients, 1 h after the start of surgery to maintain the MAP near 80 mmHg and decrease the heart rate which had not responded to an additional dose of fentanyl. None of the patients in the clonidine group needed a beta-blocker. This difference was found to be statistically significant (*P* < 0.05). No patient in either of the groups needed treatment for hypotension with ephedrine [Table 4].

The difference in the surgical grades between the two groups was found to be statistically significant (*P* < 0.05), with more patients in the diazepam group having a higher grade (more bleeding) and vice versa as shown in Table 5.

One patient in group diazepam had to be excluded from the study as additional measures were needed to optimize the blood pressure.

Discussion

The results of our study show that a better surgical field with lesser rate of surgical blood loss and shorter surgical time was obtained after oral clonidine premedication as compared to oral diazepam premedication in intravenous anesthesia (IVA) with propofol for FESS surgeries.

Blackwell *et al.* had first suggested that propofol might reduce the amount of blood loss for endoscopic sinus surgery (ESS) in comparison to isoflurane.[4] In addition,

IVA results in less bleeding and a better surgical condition for patients undergoing ESS than conventional balanced anesthesia, was proven by Ahn *et al.* in their study.[1] We, therefore, used IVA with propofol in both the groups in our study. Controlled hypotension was thought to be required to provide a dry surgical field and reduce the amount of blood loss during any surgical procedure, especially during FESS, where even a small amount of bleeding can adversely affect the surgeon's ability to visualize the surgical area. However, controlled hypotension is known to increase the risk of organ ischemia and besides blood pressure and intraoperative bleeding may not be necessarily related and hypotension by itself does not necessarily improve the surgical field.[1]

Inhalational agents cause a dose-dependent decrease in systemic vascular resistance which leads to the reduction in blood pressure and can cause a capillary bleeding in spite of the low systolic blood pressure. In the study by Wormald *et al.* it was suggested that the decrease in the MAP in the titrated total intravenous anesthesia (TIVA) group resulted in a better surgical field as compared to the sevoflurane group.[5] The mean arterial blood pressure was measured and maintained between 70 and 80 mmHg in our study.

Clonidine is an alpha-2 adrenergic agonist, which has been used as a centrally acting antihypertensive drug. Studies have demonstrated it to have sedative, anxiolytic, analgesic, and anesthetic-sparing (it reduces the dose of anesthetic and analgesics used intra- and post-operatively) effects, and it also stabilizes the circulatory system and reduces perioperative stress response.[6]

Clonidine is known to reduce both central sympathetic outflow and release of noradrenaline from peripheral presynaptic terminals.[7] It is known to decrease the heart rate due to the reduction of the sympathetic outflow, the simultaneous increase of parasympathetic tone of central origin, and due to its the influence on neurons which receive baroreceptor afferents.[8] Furthermore, being an alpha-2 adrenoceptor agonist, which modulates tonic and phasic blood pressure control, it causes a reduction in blood pressure. Both these properties (reduction

in heart rate and blood pressure) being at least partly necessary for reduction in bleeding and provision of better surgical field could be obtained by TIVA with propofol and enhanced by clonidine.

Clonidine has also been shown to potentiate postjunctional alpha-1 adrenoceptor-mediated vasoconstriction.[6] The exact mechanism of potentiation of vasoconstriction by clonidine remains unclear. Although Tanaka and Nishikawa attribute this vasoconstrictive action of clonidine to postjunctional alpha-1 adrenoceptor agonism,[9,10] Talke *et al.* suggested that clonidine acts on the alpha-2b subtype of alpha-2 adrenoreceptors in peripheral vascular smooth muscle to cause vasoconstriction.[11]

A study using a beta-blocker as premedication has shown a correlation between the surgical scores and heart rate, but not MAP.[12] Clonidine is thus capable of causing peripheral blood vessel constriction, reduction in systemic blood pressure, and heart rate which could potentially reduce bleeding during FESS and stabilize the intraoperative hemodynamic profile of the patient.[13]

One of the factors which can affect the surgical field is the severity of the chronic sinusitis.[1] Ahn *et al.*, found that the patients with a low LM-CT score (≤12) were not affected by anesthetic methods whereas TIVA resulted in a better surgical condition than conventional balanced anesthesia in patients with high-LM score (>12).[1] In our study, the patients with high LM-CT score and low LM-CT score were distributed equally between the two groups thereby negating the influence of the disease on bleeding and surgical grade in the two groups.

Contrary to what was proven by a study by Raval and Mehta[14] on inter group comparison, after 90 min of premedication, our study did not show any significant changes in the pulse rate after clonidine as compared to diazepam. Another study by Matot *et al.* has also shown that heart rate between the clonidine premedicated group and placebo-premedicated group did not differ on arrival to the operation theatre.[15] Our investigation revealed, a significant difference in the pulse rate between 15 min and 2 h 30 min, the time interval when most of the surgical intervention was in progress. However, in our study, two patients from the clonidine group needed treatment for bradycardia. The bradycardia could have been attributed to the use of propofol infusion. However, as the propofol infusion was used in both the groups, this reduced heart rate seems to be related to use of clonidine. In the study by Matot *et al.*, the patients in the clonidine group exhibited a significantly lower heart rate, though none of them needed treatment for bradycardia.[15]

The mean arterial blood pressure was significantly lower in our clonidine group, which is concurrent with the findings of Matot *et al.*[15] While two patients from the clonidine group in the above study had to be treated for hypotension following induction,[15] none of the clonidine premedicated patients in our study needed any treatment for hypotension other than intravenous fluid infusion.

Our study showed a significant decrease in the requirement of propofol infusion rate in the clonidine group compared to the diazepam group to maintain the vital parameters in the target range which is similar to the study by Matot *et al.*[15] In a study by Taghipour Anvari *et al.*, an anesthetic and analgesic-sparing effect of clonidine, was noted.[6] In our study, though more number of patients in the diazepam group required an additional dose of fentanyl to maintain the heart rate and MAP in the target range, the difference in the use was not significant between the two groups.

Our study showed significantly more number of patients with better (lower) surgical grades and higher surgeon satisfaction in the clonidine group as compared to the diazepam group, which was similar to the findings by Mohseni and Ebneshahidi.[16] The rate of bleeding was lower in the clonidine group and the difference was statistically significant. Since the duration of surgery varied among the patients in both the groups, calculation of the amount of blood lost was made more accurately as rate of blood loss.

Taghipour Anvari *et al.* have proven that oral clonidine premedication as an adjunct to remifentanil resulted in significantly less blood loss during posterior spine fusion.[6] Clonidine reduced intraoperative blood loss at the same levels of blood pressure as the control group, as the remifentanil dose was adjusted in both groups to the same target MAP of 60-70 mmHg. This finding was similar to results by Okuyama *et al.*, who observed that clonidine and prostaglandin E1 reduce blood loss during paranasal sinus surgery without inducing hypotension.[17] This study stated that clonidine constricts peripheral blood vessels and reduces nasal mucous blood flow which accounts for the reduction of blood loss.[17]

Lee *et al.*, also noted differing paraspinal muscle blood flow at the same levels of hypotension with various drugs; thus, it appears that different drugs affect tissue blood flow and that blood loss occurs through mechanisms other than blood pressure reduction.[18] Thus, it is possible that clonidine has the same effect at higher blood pressure, which can obviate the need for hypotensive anesthesia.[6]

Similar to a recent study by Wawrzyniak *et al.*,[12,13] the duration of surgery in our study was found to be 111 min versus 136 min in the clonidine and diazepam group, respectively. This difference was found to be statistically significant.

We decided to use 4 mcg/kg clonidine in our study as higher doses may cause α stimulation which may result in an increase in the blood pressure. In most human studies, 4 μ/kg has been applied without any signs of α stimulation.[15]

Conclusion

The endoscopic approach for surgery in chronic sinusitis is performed close to the skull base and the orbital wall and requires a bloodless surgical field. Our study has shown that a change in the drug used for premedication can make a significant difference in the hemodynamic profile, thus providing a better surgical field with less blood loss and shorter surgical time. However, this study did not specifically take into consideration whether premedication with clonidine can provide any advantage specifically in difficult ESS cases with LM-CT score of >12 for which further studies might be required.

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Conflicts of interest

There are no conflicts of interest.

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