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Evaluation of Oral Clonidine Premedication on Intraoperative Blood Loss and Bleeding Severity Score in Functional Endoscopic Sinus Surgery – A Prospective Placebo Controlled Study

Masrat Jan[1*], Fayaz A. Reshi [1], Shiwalika Gupta[1], Shaugfta Aara[2] Iftikhar H. Wani[3] and Basharat Saleem[1]

[1]Department of Anaesthesiology and Critical Care Medicine, Government Medical College Srinagar, Kashmir, India.
[2]Department of Physiology, Government Medical College Jammu, J & K India.
[3]Government Hospital for Bone and Joint Surgery, Barzulla, Srinagar, Kashmir, India.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MJ and FAR designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors SG and SA managed the analyses of the study. Authors IHW and BS managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Background: Bleeding during functional endoscopic sinus surgery (FESS) remains a challenge for both surgeons and anaesthesiologists despite several modalities available for improving the surgical field. This study was conducted to evaluate the effect of oral clonidine premedication on blood loss and the quality of the surgical field in FESS.
Methods: This prospective placebo controlled trial was performed on 120 patients (ASA I, ASA II). Patients undergoing endoscopic sinus surgery for chronic sinusitis and nasal polyposis were randomly allocated to receive either oral clonidine 0.005mg/kg or identical-looking placebo tablets 90 min before arrival at the operating room. During general anaesthesia, the hemodynamic endpoint of the anaesthetic management was

**Corresponding author: Email: drjmasrat@yahoo.com;*

maintenance of hypotension (Mean Arterial Presure) at ≤ 65 mmHg for producing a bloodless surgical field. The control of MAP was attained with inspired concentration increments of halothane up to maximum of 1.5 vol % as needed. Intraoperative bleeding was assessed on a six – point scale from 0 (= no bleeding) to 5 (= severe bleeding). Data were compared with chisquare test, fisher's exact test and Student t-test.
Results: There was less bleeding volume in the clonidine group (mean±SD) than in the placebo group (140.7±65.4 Vs 199.2±104.4, P<0.05). Frequency of bleeding severity scores 3 and 4 (troublesome with repeated suction) were lower in the clonidine group than in the placebo group (13.3 Vs 33.3%, P< 0.05).). Accordingly, the surgeon was more satisfied with the surgical field in the clonidine group than with that in the placebo group.
Conclusion: In conclusion, premedication with oral clonidine can effectively reduce bleeding during endoscopic sinus surgery.

Keywords: Controlled hypotension; sinus surgery; bleeding severity score; clonidine.

1. INTRODUCTION

Functional endoscopic sinus surgery has been a major advancement in the management of chronic sinusitis and other sino-nasal diseases [1]. Over the past two decades, a considerable interest in endoscopic surgery of the paranasal sinuses has been expressed [2]. There are some limiting factors in this surgery [3] and the main consideration is blood loss because the mucosa is highly rich in blood vessels [4]. Excessive intraoperative bleeding may result from injury to blood vessels resulting in impaired visibility during surgery [5]. Serious complications usually result from impaired visibility due to excessive bleeding during surgery. To avoid such complications, endoscopic sinus surgery can be performed either with local anesthesia [6], with vasoconstrictors (e.g. epinephrine, cocaine and phenylephrine) [7,8,9], or under general anesthesia supplemented with controlled hypotension [10]. Several reports have shown various techniques for diminishing intraoperative bleeding [11,12,13]. Although, hypotensive anesthesia may decrease intraoperative bleeding, it is not confirmed in some studies [14,15].

Clonidine is a centrally acting α 2 agonist useful as a premedication as it also decreases analgesic consumption [16], postoperative nausea, vomiting [17] and shivering [18]. It has antihypertensive property by decreasing sympathetic outflow [19]. The use of drugs such as oral clonidine given before operation would be desirable to enhance the hypotensive action of inhalation agents without disadvantages of intravenous vasodilators [20,21]. Oral clonidine premedication significantly reduced bleeding in middle ear microsurgery and intraoperative bleeding was assessed on a four point scale by a surgeon, but blood volume was not estimated [22,23]. Accordingly, we designed a prospective randomized study to investigate the effects of clonidine premedication on –

1. Intraoperative bleeding volume (ml) in patients undergoing endoscopic sinus surgery.
2. Bleeding severity scoring.

2. MATERIALS AND METHODS

After approval by institutional committee and written informed consent, a prospective placebo controlled clinical study “Evaluation of oral clonidine premedication on intraoperative

blood loss and bleeding severity score in Functional Endoscopic Sinus Surgery" was conducted on patients electively scheduled for FESS. Among !50 patients who were planned for surgery, only 120 met our inclusion criteria.

Patients of ASA I and ASA II between 18 to 60 years of age of either sex were included in the study. Patients receiving drugs having effect on autonomic nervous system e.g. β-blockers (e.g. esmolol, propanolol) and those which influence blood coagulation that is Anticoagulants (e.g. warfarin), platelet aggregation inhibiting drugs (e.g. ticlopidine, clopidogrel, abciximab, aspirin), and on long standing corticosteriod therapy were excluded from the study. After proper case selection, patients were randomly assigned to 2 equal groups (n=60). Patients were allotted to either group by a set of random numbers by an independent investigator. The numbers were kept equal by means of permuted randonmisation. The patient, anaesthetist and surgeon were blinded for the treatment.

Group I (Clonidine Group): Clonidine group patients were given oral clonidine 5μg/kg 90 minutes before operation.

Group II (Control Group): Control group patients were given tablet Famotidine 40mg 90 minutes before operation as a placebo having similar color and shape to clonidine preparation.

Procedure of anaesthesia was discussed with patient and his/her consent for participation in the study was taken. Patients were kept 6-8 hours fasting. Peripheral line was secured on upper limb, preferably on dorsum of hand or lateral aspect of forearm. Monitors were attached for standard monitoring of vital signs (Heart Rate, ECG, NIBP, SPO_2).

All patients received phenylepherine nasal drops 0.5% fifteen minutes before induction of anaesthesia in order to shrink nasal mucosal vessels. Patients were preoxygenated with 100% oxygen for 2-3 minutes with mask ventilation. Anaesthesia was induced with injection thiopentone sodium 5mg/kg,inj fentanyl 2μ/kg followed by injection suximethonium 1.5mg/kg body weight and patients were intubated with appropriate size cuffed polyvinyl chloride endotracheal tube. Systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were recorded 2 hours before surgery, at the time of anaesthesia induction and 2 and 5 minutes after induction of anaesthesia. Blood pressure was recorded directly after every 5 minutes with an arterial line. Heart rate and SPO2 was recorded every time. To maintain effective hypotension for producing a bloodless surgical field, mean arterial pressure was kept around 65mmHg. The direct control of mean arterial pressure was attained with increasing inspired concentration of halothane up to maximum of 1.5 vol% as needed .Patients were considered failed cases when mean arterial pressure(MAP) was not reached 65 mmHg within 10 minutes. Surgeons were unaware of the two groups. Intraoperative bleeding was assessed as per the scoring scale below:

0 No bleeding
1 Slight bleeding, no suctioning of blood required.
2 Slight bleeding occasional suctioning required. Surgical field not threatened.
3 Slight bleeding, frequent suctioning required. Bleeding threatened 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, constant suctioning required. Bleeding appeared faster than could be removed by suction. Surgical field severely threatened and surgery not possible [7].

At the end of surgery, bleeding volume was measured with graduated suction bottle.

3. RESULTS

There were no significant differences in mean age, weight, sex, preoperative MAP, pulse rate and frequency distribution of operation indications (Table 1).

Table 1. Comparing the demographic and clinical characteristics in two groups

	Clonidine group	Placebo group
Number	60	60
Age	34.8 ± 11.3	33.9 ±10.8
Sex-male/female ratio	1.66	1.64
Weight	64.4±9.6	62.9±7.6
Preoperative HR	78.6 ±6.5	79.3 ±6.7
Preoperative MAP	89.4±3.6 mmHg	90.4±6.1mmHg
Disease (percent)		
Unilateral polyposis	38.3	45.0
Bilateral polyposis	26.7	26.7
Unilateral sinusitis	16.7	11.7
Bilateral sinusitis	11.7	16.7

The average intraoperative bleeding severity score for the clonidine group was lower than that for the placebo group (P<0.05). Also, frequency of bleeding severity with score of 1 in the clonidine group (slight bleeding; no suctioning of blood required) was significantly greater than that of placebo group (P<0.05). Number of patients in the clonidine group with category score of 3 and 4 (bleeding threatened surgical field) were less than placebo group (P<0.05). None of patients in the two groups, did not have score of 0 (no bleeding) and 5 (severe bleeding; surgery not possible) (Table 2).

Table 2. Intraoperative bleeding severity score

Intraoperative Bleeding Severity Score						
		Clonidine		Placebo		p
		n	%	n	%	value
Intraoperative bleeding severity score	Grade I	35	58.3	28	46.7	0.011
	Grade 2	17	28.3	12	20.0	(Sig)
	Grade 3	8	13.3	11	18.3	
	Grade 4	0	0.0	9	15.0	

The average intraoperative blood loss (ml) in clonidine was 140.7 ±65.4 while as in placebo group the average intraoperative blood loss(ml) was 199.2 ±104.4. This difference in blood volume loss during surgery was statistically significant (p value <0.05) (Fig. 1).

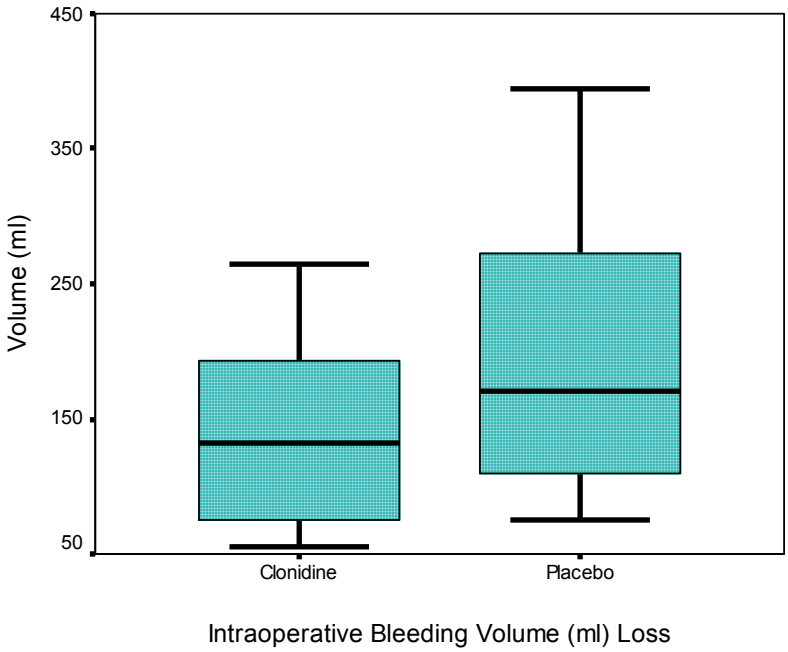

Fig. 1. Data were expressed as median ± standard deviation (SD) or absolute values. Qualitative data were compared with the chi-square test and fisher's exact test. Quantitative variables were compared with the Student t test. The level of statistical significance was set at P < 0.05

4. DISCUSSION

During endoscopic sinus surgery, the most important and common complication is excessive bleeding [4,24]. Controlled hypotension is applied to reduce bleeding as an aid to surgery in patients undergoing middle ear and nasal surgery, neurosurgery, orthopedic operations, head and neck surgery and in plastic surgery [25]. Clonidine, a potent suppressor of sympathoadrenal activity, has been given orally before operation to augment the hypotensive action of isoflurane [20,21]. Other studies have shown the effect of this drug on reduction of bleeding in patients undergoing middle ear microsurgery and also decreasing the need for using other drugs (e.g. Isoflurane, fentanyl, and urapidil) for inducing hypotension [22,23]. Clonidine has been found to suppress central noradrenergic hyperactivity with secondary attenuation of peri-operative hemodynamic instability [26,27].

With this background in mind the present placebo controlled trial was undertaken to evaluate the effectiveness of oral Clonidine premedication in controlling intraoperative bleeding volume and its severity. In this context, various parameters were obtained which are as under;

There was no significant difference between the groups among the demographic variables like age, gender, weight, duration of surgery and pre-operative clinical parameters such as pulse, blood pressure and SPO2.

4.1 Mean Arterial Presure

There was no statistically significant difference in pre operative Mean arterial pressure of the two groups (89.4±3.6 versus 90.4±6.1 p >0.05). Patients receiving clonidine exhibited a significant decrease in mean arterial pressure (89.4±3.6 to 76.7±3.9) compared with placebo group (mean arterial pressure 90.4±6.1 to 91.5±5.7) at 0 minutes and throughout the procedure it was statistically significant (Fig. 2).

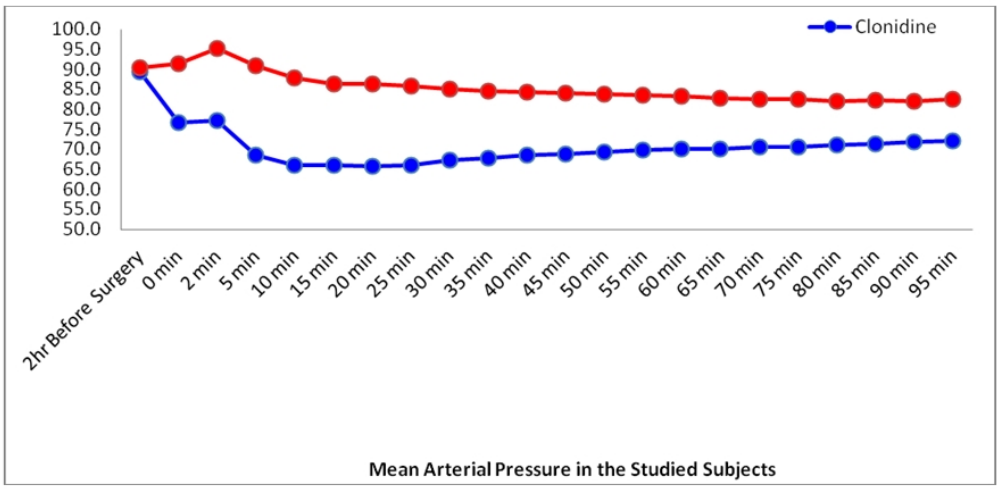

Fig. 2. Mean arterial pressure in the studied subjects

The slight increase in mean arterial pressure in placebo group at zero minute could be because of apprehension while the same was blunted in the clonidine premedicated patients by the anxiolytic and sedative effect of clonidine. Moreover, Clonidine attenuates the increase in sympathoadrenal response associated with intubation in clonidine premedicated patients. This was in agreement with the studies by Pouttu et al. [26]. The peak decrease in MAP occurs at 10 minutes of the procedure more so in clonidine group than in placebo group. This is because of the additive effect of clonidine with increasing volume concentrations of halothane and fentanyl. These findings were consistent with the studies by Ghignone et al. [28] , Pouttu et al. [26], Welfringer et al. [23], Kumar A Boss et al. [29], Filos et al. [30], Davood Attaran et al. [31] and Ebneshahidi et al. [32].

4.2 Intraoperative Bleeding

The mean (range) bleeding volume in the clonidine group was significantly lower than that in the placebo group (140.7 ±65.4 versus 199.2±104.4, p < 0.0001) (Table 3).

Table 3. Intraoperative Bleeding Volume Loss

		Clonidine group	Placebo group	P value
Intraoperative Bleeding volume (ml) loss	mean ± SD	140.7 ±65.4 (55,265)	199.2 ±104.4 (75,395)	0.000 (Sig)

This is because clonidine acts by central α2 adrenoreceptor stimulation, resulting in diminished sympathetic outflow [20] and also stimulates parasympathetic outflow, which may contribute to the slowing of heart rate as a consequence of increased vagal tone and diminished sympathetic drive [33]. Moreover, clonidine has been shown to exhibit anaesthetic, sympatholytic and analgesic properties [34] with additive effect of increasing supplements of halothane and fentanyl. Our results were consistent with studies by Welfringer et al. [23], Marchal et al. [22] ,Hajy Mohammad et al. [35], Kazuhiko Okuyama et al. [36], Hassanali Sultani et al. [37], Ebneshahidi et al. [32] and Mohseni et al. [38].

4.3 Intra-operative Bleeding Severity Score

Frequency distribution of bleeding with scores of 3 and 4 were significantly lower in the Clonidine group compared to the Placebo group (13.3% versus 33.3%, $p < 0.05$). These findings were similar to the findings of Marchal et al. [22] and Welfringer et al. [23] studies. It may possibly be due to hemodynamic attenuation with clonidine as diminished sympathetic outflow results from central α 2 adrenoreceptor stimulation, thus reducing bleeding 22, 30, 31.The findings of this study were consistent with the studies by Hajy Mohammad et al. [35], Hassanali Sultani et al. [37] and Mohseni et al. [38].

5. CONCLUSION

In conclusion the present placebo controlled study shows that Oral premedication with clonidine, 90 minutes before operation reduces bleeding during endoscopic sinus surgery with halothane under general anaesthesia and provides a clear field for surgery. Accordingly, the surgeon was more satisfied with the surgical field in the clonidine group than with that in the placebo group. Therefore, use of this drug is effective in reducing intraoperative bleeding and its severity in endoscopic sinus surgery.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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