Original Article

Oral Clonidine Premedication Decreases Intraoperative Bleeding in Patients Undergoing Endoscopic Sinus Surgery

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ABSTRACT

Background: The antihypertensive drug, clonidine, is a centrally acting alpha 2 agonist, useful as a premedication because of its sedative and analgesic properties. We examined the effect of clonidine given as an oral premedication in producing a bloodless surgical field in patients undergoing endoscopic sinus surgery. We also evaluated the relation between bleeding volume and consumption of fentanyl and hydralazine to control hypotension.

Methods: This prospective double - blinded clinical trial was performed on 113 patients (ASA I, ASA II). Fifty-two patients received oral clonidine (5 μ g/kg) while the other 61 patients received placebo. During general anesthesia, the hemodynamic endpoint of the anesthetic management was maintenance of hypotension (MAP) at 70 mmHg for producing a bloodless surgical field. The direct control of MAP was attained with inspired concentration increments of halothane up to maximum of 1.5 vol % as needed. When it was unsuccessful, an intravenous fentanyl bolus of 2 μ g/kg was also added. When both drugs failed, hydralazine , was given intravenously as a bolus and intermittently, 0.1mg/kg up to a maximum dose of 40 mg. Intraoperative bleeding was assessed on a six – point scale from 0 (= no bleeding) to 5 (= severe bleeding). Data were compared with chi-square test, fisher's exact test and Student t-test.

Results: There was less bleeding volume in the clonidine group (mean $\pm$ SD) than in the placebo group (144 $\pm$ 75 Vs 225 $\pm$ 72 ml, 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 (12% Vs 35%, P< 0.05). Fentanyl requirement was significantly lower (112 $\pm$ 18 Vs 142 $\pm$ 21 μ g, P < 0.05) in the clonidine group. Hydralazine requirement was significantly lower (0.45 $\pm$ 1.68 Vs 2.67 $\pm$ 4.33 mg, P<0.05) as well.

Conclusion: Premedication with oral clonidine reduces bleeding in endoscopic sinus surgery and also decreases fentanyl, and hydralazine consumption for controlling hypotension.

Key words: Sinus surgery, Endoscopy, Clonidine, Hydralazine, Fentanyl, Bleeding

Over the past two decades, a considerable interest in endoscopic surgery of the paranasal sinuses has been expressed [1]. There are some limiting factors in this surgery [2] and the main consideration in that is blood loss because the mucosa are highly rich in blood vessels[3]. Operative bleeding results from cutting vessels which may be arteries; capillaries or veins [4]. 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 [5] , with vasoconstrictors (e.g. epinephrine, cocaine and phenylephrine) [6,7,8], or under general anesthesia supplemented with controlled hypotension [9]. Several reports have shown various techniques for diminishing intraoperative bleeding [10,11,12].

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Many surgeons prefer general anesthesia to local anesthesia [3, 13, 14]. Although, hypotensive anesthesia may decrease intraoperative bleeding, it is not confirmed in some studies [15, 16]. Severe hypotension may occur due to potent and rapid effect of intravenous antihypertensive drugs [17]. So direct monitoring of arterial pressure is mandatory.

Clonidine is a centrally acting α_2 agonist useful as a premedication as it also decreases analgesic consumption[18], postoperative nausea, vomiting [19] and shivering [20]. It has antihypertensive property with decreasing sympathetic outflow [21]. 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 [22, 23]. In the past two studies, premedication with oral clonidine significantly reduced bleeding in middle ear microsurgery. Intraoperative bleeding was assessed on a four point scale by a surgeon, but blood volume was not estimated [24,25]. Accordingly, we designed a randomized double –blind study to investigate the effects of clonidine premedication on:

1) intraoperative bleeding volume (ml) in patients undergoing endoscopic sinus surgery
2) bleeding severity scoring
3) antihypertensive drugs requirement.

Materials and Methods

After obtaining approval from the Ethics Committee and receiving signed letters of informed consent, 113 ASA I, II patients were scheduled for elective endoscopic sinus surgery under general anesthesia.They were put into a prospective, double - blind clinical trial.

The patients were between 18 and 70 years old. Patients receiving autonomic nervous system active drugs, agents influencing blood coagulation and long-standing corticosteroids were excluded. They were randomly divided to clonidine (N =52) and control (N = 61) group. Fasting time and fluid therapy were similar in both groups. NPO duration was eight hours and fluid replacement was based on 4.2.1 rule [26]. Clonidine group patients received oral clonidine 5 μg/kg, 90 minutes before operation. This period ensures maximum plasma concentrations after oral ingestion of the drug. Control group received placebo with similar color and shape to clonidine prepration. All patients received phenylephrine drop 0.5% fifteen minutes before induction of anesthesia in order to shrink nasal mucosal vessels. Anesthesia was induced with thiopental sodium 5mg/kg, fentanyl 2μg/kg and pancronium bromide 0.1mg/kg. Then laryngoscopy was performed and the trachea was intubated after 3 minutes of mask ventilation in all patients. Ventilation was controlled with tidal volume: 10 ml/kg and respiratory rate of 10 breaths /minute. Anesthesia was maintained with 50/50 v/v mixture of oxygen, nitrous oxide, and halothane up to 1.5vol%. Mean arterial blood pressure was recorded 2 hours before surgery, at the time of anesthesia induction and 2 and 5 minutes after induction of anesthesia.

The blood pressure was measured directly every 10 minutes with an arterial line. Heart rate was recorded every time. To maintain enough hypotension for producing a bloodless surgical field, mean arterial pressure was proposed to be 70mmHg [26]. The direct control of MAP was attained with inspired concentration increments of halothane up to maximum of 1.5vol% as needed. After 10 minutes if it was unsuccessful, intravenous fentanyl bolus of 2μg/kg was also added [27]. When both drugs failed to provide the desirable hypotension in 10 minutes, hydralazine, a direct relaxant of muscle tone and antihypertensive drug [28] was given as a bolus and intermittently 0.1mg/kg up to a maximum dose of 40mg. When the measured MAP did not reach the end point pressure, blood pressure was reduced with other agents such as sodium nitroproside. Then operation was continued. Patients were considered as failed cases when other drugs were used to induce hypotension or when operation finished before reaching target blood pressure. The same surgeon performed all the operations to ensure consistency in the estimation of surgical field. He was blinded to the two groups. Intraoperative bleeding was assessed according to 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[4].

At the end of surgery, bleeding volume (ml) measured with scaled bottle.

Data were expressed as mean ± 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 $P < 0.05$.

Results

There were no significant differences in mean age and weight, sex, preoperative MAP and pulse rate, duration of surgery and frequency distribution of operation indications (Table 1).The average category scale 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). The number of patients who were excluded from the study in the clonidine group was 3 (6%) while in the placebo group it rose to 19 cases (31%).This figure was significantly lower in the clonidine group ($P<0.05$). Mean bleeding volume (ml) was significantly lower in the clonidine group than in the control group (144 ± 75 vs 225 ± 72, $P<0.05$). There was no significant difference in mean intraoperative consumption of halothane between the two groups. Mean fentanyl and hydralazine requirements were significantly lower in patients who had received clonidine than those in the control group ($P<0.05$) (Table 2).

Discussion

During endoscopic sinus surgery, the most important and common complication is excessive bleeding[3,29]. 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 [26].

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

	Clonidine group	Placebo group
N	52	61
Age (yr.)	43 ± 12	39 ± 12
Weight (kg)	71 ± 11	68 ± 10
Sex (M:F)	1.88	1.65
Preoperative MAP (mmHg)	88 ± 8	92 ± 8
Preoperative PR (beats/min)	82 ± 7	80 ± 9
Operating time (minutes)	55 ± 17	61 ± 23
Disease (n, percent):		
Unilateral polyposis	29(56%)	37(60%)
Bilateral polyposis	9(18%)	14(23%)
Unilateral sinusitis	5(10%)	5(8%)
Bilateral sinusitis	6(12%)	4(7%)
Mucocle	2 (4%)	1 (2%)

n= number, M:F= male/female ratio, MAP= mean arterial blood pressure, PR= pulse rate
Values are means ±SD or n (%) where appropriate

Table 2. Comparing the bleeding severity and requirements during endoscopic sinus surgery in two groups

	Clonidine group	Placebo group
Bleeding severity *		
Grade I	21 (40%)	11(18%)
Grade II	25 (48%)	29 (47%)
Grade III	6(12%)	15 (25%)
Grade IV	0	6(10%)
Mean	1.71 ± 0.4	2.26 ± 0.6
Halothane consumption (N, %)		
<1%	9 (17%)	8 (13%)
1-1.5%	43 (83%)	53 (87%)
Mean (%)	1.32 ± 0.24	1.35 ± 0.21
Fentanyl consumption (N, %) **		
Use	26 (50%)	48 (79%)
No use	26 (50%)	13 (21%)
Mean (µg)	112 ± 18	142 ± 21
Hydralazine consumption (N, %) **		
Use	3 (6%)	19 (31%)
No use	49 (94%)	42 (69%)
Mean (mg)	0.4 ± 1.68	2.67 ± 4.33

*P<0.05, T- test, Pearson chi-square
**P<0.05, T- test, Fisher's exact test, Pearson chi-square

Clonidine, a potent suppressor of sympathoadrenal activity, has been given orally before operation to augment the hypotensive action of isoflurane [22, 23]. 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[24,25]. Clonidine has been found to suppress central noradrenergic hyperactivity with secondary attenuation of perioperative hemodynamic instability [30, 31]. In this study, the effect of oral premedication on intraoperative bleeding in endoscopic sinus surgery was studied. Frequency distribution of bleeding with scores of 3 and 4 were significantly lower in the clonidine group compared to the placebo group. These findings were similar to the findings of marchal et al and welfringer et al studies[24,25]. Also, mean intraoperative bleeding volume was less in the clonidine group than in the control group. 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]. In our study , there was no statistically significant difference in halothane requirement between the two groups. In the prospective study of marchal et al in 2001, intraoperative consumption of isoflurane was lower in patients premedicated with clonidine than in control patients undergoing middle ear microsurgery [24]. This difference is due to pharmacologic characteristics of isoflurane which reduces blood pressure more than halothane [23]. However, in the first step, using more halothane, (1-1.5 vol%) 50 percent of patients in clonidine group reached the target MAP (70 mmHg) while it happened only in 21% of patients in the placebo group. Other patients required another drug (fentanyl) to achieve the satisfactory level of hypotension (Table 2). In the clonidine group, fentanyl requirement was also significantly lower as compared to the placebo group. This result was similar to marchal et al study. That is due to clonidine pharmacologic properties including antihypertensive [22] and analgesic effects [18,33]. Mean amount of hydralazine to reach target blood pressure was less in the clonidine group than in the control group. This finding was in agreement with marchal's study on urapidil to decrease blood pressure which could be explained with the lowering

effect of clonidine on blood pressure.. The number of excluded patients was significantly less in the clonidine group than in the placebo control group.

In summary, the present prospective randomized, double–blind, placebo–controlled study shows that oral premedication with clonidine, 90 minutes before operation, provides a clear field for surgery and reduces bleeding during endoscopic sinus surgery with halothane under general anesthesia. Clonidine also reduces the need for antihypertensive drugs to control hypotension. Therefore, use of this drug is effective on reducing intraoperative bleeding in endoscopic sinus surgery.

References

1. *Rice DH: Endoscopic sinus surgery. In: Donald PJ, Gluckman Jl, Rice DH. The sinuses, New York: Raven press, p 255, 1995.*
2. *Sun S. Intraoperative complications of endoscopic sinus surgery. Zhonghua Er Bi Yan Hou Ke Za Zh 36(5):335-7, 2001.*
3. *Joseph MM: Anesthesia for ear, nose and throat surgery. In: Longneeker DE., Tinker JH, Morgan GE. Principles and practice of Anesthesiology, 2 nd ed. st Louis: Mosby, p 2210, 1998.*
4. *Andre PB. Comparison of sodium nitroprosside and esmolol induced controlled hypotension for functional endoscopic sinus surgery, Canadian journal of anesthesia, V: 42, N; 1995.*
5. *Fedok FG, Ferraro RE, Kingsley CP, Fornadley JA. Operative times, postanesthesia recovery times, and complications during sinonasal surgery using general anesthesia and local anesthesia with sedation. Otolaryngol Head Neck Surg 122(4):560-6, 2000.*
6. *Friedman M, Venkatesan TK, Lang D, Caldarelli DD. Bupivacaine for postoperative analgesia following endoscopic sinus surgery. Laryngoscope 106(11):1382-5, 1996.*
7. *Kubo N, Nakamura A, Yamashita T. Efficacy and complications of topical cocaine anesthesia in functional endoscopic sinus surgery. Nippon Jibiinkoka Gakkai Kaiho 98(8):1263-9, 1995.*
8. *Riegle EV, Gunter JB, Lusk RP, Muntz HR, Weiss KL.Comparison of vasoconstrictors for functional endoscopic sinus surgery in children. Laryngoscope 102(7):820-3, 1992.*
9. *Heermann J, Neues D: Intranasal microsurgery of all paranasal sinuses, the septum and the lacrimal sac with hypotensive anesthesia, Ann orol rhinol laryngol, 95: 631-638, 1999.*
10. *Terrell JE, Brown ACD: endoscopic sinus surgery. In: Bready LL, Mullins AM. eds. Decision making in anesthesiology . 3 rd ed. London: Mosby, p 526, 2000.*
11. *Eberhart LH, Folz BJ, Wulf H, Geldner G. Intravenous anesthesia provides optimal surgical conditions during microscopic and endoscopic sinus surgery. Laryngoscope 113(8):1369-73, 2003.*
12. *Jacobi K, Rickauer AJ. Prophylactic analgesia in functional endoscopic sinus surgery. Hemodynamics, surgical conditions, stress response. Anasthesiol Intensivmed Notfallmed Schmerzther 34(5):278-87, 1999.*
13. *Danielsen A, Gravningsbraten R, Olofsson J. Anaesthesia in endoscopic sinus surgery. Eur Arch Otorhinolaryngol 260(9):481-6, 2003.*
14. *Gittelman PD, Jacobs JB, Skorina J.Comparison of functional endoscopic sinus surgery under local and general anesthesia. Ann Otol Rhinol Laryngol 102(4 Pt 1):289-93, 1993.*
15. *Ilberg C, May A, Weber A. Microsurgery of the nasal cavity and paranasal sinuses. Laryngorhinootologie 69(1):52-7, 1990.*
16. *Jacobi KE, Bohm BE, Ricaver AJ, Jacobi C, Hemmeling RM. Moderate controlled hypotension with sodium nitroprosside dose not imporve surgery. J clin Anesth, 12(3): 202-7, 2000.*
17. *Wasserstrum N. Nitroprusside in preeclampsia. Circulatory distress and paradoxical bradycardia. Hypertension 18(1):79-84. 1991.*
18. *Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY. Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Sin 38(1):23-9, 2000.*
19. *Handa F, Fujii Y.The efficacy of oral clonidine premedication in the prevention of postoperative vomiting in children following strabismus surgery. Paediatr Anaesth 11(1):71-4, 2001.*
20. *Mao CC, Tsou MY, Chia YY, Chow LH, Chan KH, Lee TY.Pre-anesthetic oral clonidine is effective to prevent post-spinal shivering. Acta Anaesthesiol Sin 36(3):137-42, 1998.*
21. *Gavras I, Manolis AJ, Gavras H.The alpha2 -adrenergic receptors in hypertension and heart failure: experimental and clinical studies. J Hypertens 19(12):2115-24, 2001.*
22. *Toivonen J, Kaukinen S. Clonidine premedication: a useful adjunct in producing deliberate hypotension. Acta Anaesthesiol Scand 34(8):653-7, 1990.*

23. Wookcock TE, Millard RK, Dixon J,prys-roberts C. Clonidine premedication for isoflurane-induced hypotension. Sympathoadrenal responses and a computer-controlled assessment of the vapour requirement. Br J Anesth 67:11-19, 1987.
24. Marchal JM, Gomez – lugue A, Martos-Crespo F, Sanchez De La Cuesta F, Martinez-lopez MC, .Delgado-Marinez AD. Clonidine decreases intraoperative bleeding in middle ear microsurgery. Acta anaesthesiol scand 45(5): 627-633, 2001.
25. Welfringer P, Manel J. Clonidine premedication and isoflurance anesthesia to reduce bleeding in otologic surgery, Ann Fr anesth reanim, 11(2): 125-31, 1992.
26. Aken HV, Miller ED: Delibrate hypotension. In: Miller RD, cucchiara RF. eds. Anesthesia. 5 th ed. Philadelphia: cherchill livingstone, p 1470-72, 2000.
27. Joshi GP, Warner DS, Twersky RS, Fleisher LA. A comparison of the remifentanil and fentanyl adverse effect profile in a multicenter phase IV study. J Clin Anesth 14(7):494-9, 2002.
28. James DJ, Bedford RF. Hydralazine for controlled hypotension during neurosurgical operations. Anesth Analg 61(12):1016-9, 1982.
29. Sun H, Tan G, Li S, Xiao J, chen J. Complications of endoscopic sinus surgery: incidence and prevention-analysis of 307 cases, Hunan Yi Ke Da Xue Xue Bao, 23(6): 583-6; 1998.
30. Pouttu J, Rouminen M, Rosenberg PH. Effects of oral clonidine premedication on concentrations of cortisol and monoamine neuro transmitters and their metabolites in cerebrospinal fluid and plasma. Acta anaesthesiol scand 33: 137-141, 1989.
31. Quintin L, Bonuet F, Macquin I, Szekely B, Becquemin JP, Ghignone M. Aortic surgery: effect of clonidine on intraoperative catecholamineargic and circulatory stability .Acta Anaesthesiol scand 34: 132-137, 1990.
32. Schieber RA, Namnoum A, Sugden A, Shiu GK, Orr RA, Cook DR. Hemodynamic effects of isoflurane in the newborn piglet: comparison with halothane. Anesth Analg 65(6):633-8, 1986.
33. Barrera E. Samso E. Valles J. puig MM. Peroperative analgesic effects of clonidine and fentanyl administered by systemic and/or epidural routes. Br J anaesth 80: 113 A, 1998.