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Effect of Intravenous Clonidine on Stress Response in Patients Undergoing Coronary Artery Bypass Grafting

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Abstract

Introduction: Nitrous oxide has been used over decades in cardiac surgery despite of the increase in systemic and pulmonary vascular resistance it causes. We conducted this study to compare intravenous clonidine as an alternative to nitrous oxide for analgesia and anesthesia in cardiac surgeries in patients undergoing coronary artery bypass grafting.

Material and methods: This prospective randomised control trial was conducted in 50 ASA grade II and III patients aged between 40 to 70 yrs. who were posted for coronary artery bypass grafting. Patients were divided into two groups of 25 patients with one group receiving intravenous clonidine 4 µg/kg diluted in 100ml Normal Saline over 15 min, 30 min prior to induction and intraoperatively anesthesia was maintained with combination of oxygen with sevoflurane while other group received 100ml Normal Saline 30 min prior to induction and received oxygen with 50% Nitrous oxide with sevoflurane starting at induction. Attenuation of stress response to intubation, skin incision and sternotomy was assessed by measuring cardiovascular parameters.

Results: In our study groups Pulmonary vascular resistance was significantly lower in patients who received clonidine; this group also maintained a higher cardiac output than the group in which nitrous oxide was used. The systemic vascular resistance and arterial blood pressures were also lower in clonidine group however the differences were not statistically significant.

Conclusion: In this study we were able to demonstrate that intravenous clonidine has a more favourable result on cardiac variables especially in pulmonary vasculature during intubation, incision & sternotomy and that clonidine could be used for reducing the stress response in these high risk patients.

Keywords: PCWP (pulmonary capillary wedge pressure), PAP (pulmonary arterial pressure), PVR (pulmonary vascular resistance), Heart rate, cardiac output

Introduction

Cardiac surgeries are one of the most high risk procedures to be done under anesthesia with patients already having low tolerances for hemodynamic stress. Nitrous oxide has been used over decades in cardiac

surgery despite of the increase in systemic and pulmonary vascular resistance it causes[1].

Nitrous oxide is a very cheap and safe agent for anesthesia and analgesia. It has a long history of clinical use, although its use is becoming lesser in the western world because of its adverse effects on cardiac physiology[1-4] however it is still widely being used in INDIA during general anesthesia even in cardiac surgeries because of its low cost and the ability to reduce requirement of costly anesthetic agents.

Clonidine is an alpha 2 adrenergic agonist that has known analgesic and hypnotic properties and is known to reduce requirement of anaesthetic agents[5] and opioids[6,7]. Clonidine is also used as an antihypertensive and reduces blood pressure and heart rate[8,9]. In this study we specifically studied the reduction in stress response by monitoring systemic vascular resistance and pulmonary vascular resistance and PCWP in patients undergoing CABG.

Material and methods

After obtaining the approval from the ethics committee, 50 ASA grade II and III patients aged between 40 to 70 years scheduled to undergo elective coronary artery bypass grafts were enrolled in this study after inclusion criteria have been met and written informed consent obtained. The patients were randomly assigned to one of the two groups (25 patients each) according to random table created by computer.

All patients were given tablet Diazepam 5mg orally on night before surgery along with all their antihypertensive and preoperative medicines. In the morning of surgery patients were shifted to ICU after getting morning dose of their medications. Inj. Morphine 0.1mg/kg & Promethazine 25mg were given as premedication intramuscularly 45 min prior to shifting to operating room. During this period supplemental oxygen was given through oxygen mask and SpO_2 & heart rate were monitored.

In the operating room after connecting all the monitors' intravenous access was secured and arterial monitoring was established under local anesthesia by right radial artery cannulation. A flow-directed pulmonary artery catheter(Edwards life sciences 831HF75) was also placed via the right internal jugular vein under local anesthesia by lignocaine infiltration, position of catheter tip in pulmonary artery catheter was confirmed by wedge pressure ,cardiac output was measured by thermodilution using 10 ml Normal saline of 24^{o}C(Computation Constant of 0.612). Measured values from HR, BP, CVP, PAP, PCWP & CO were used to calculate CI, SVR, SVRI, PVR and PVRI

After measuring baseline values patients in first group were given intravenous clonidine 4 µg/kg in 100ml normal saline over 15 minutes while in second group all patients were given 100ml normal saline over 15 minutes. Anesthesia induction was started 15 min after baseline readings were noted.Prior to induction Inj. Morphine 0.1mg/kg was given intravenously. Induction was done with Thiopentone sodium 2-3 mg/kg given over two minutes**.** After loss of eyelash reflex patients were manually ventilated to maintain $ETCO_2$ between 30-35 mmHg. Vecuronium Bromide 0.12 mg/kg was then administered to facilitate tracheal intubation .The tracheal intubation was done after four minutes of muscle relaxant. Anesthesia was maintained with Sevoflurane + 100% O_2 in group one, while Sevoflurane + Nitrous Oxide + Oxygen (FiO_2 0.5) in second group. Inspiratory sevoflurane concentration was varied to maintain BiSpectral Index (BIS) values between 50-60 and Relaxation was maintained to single count of train of four by supplementing Vecuronium bromide throughout the period of surgery. Beat to beat

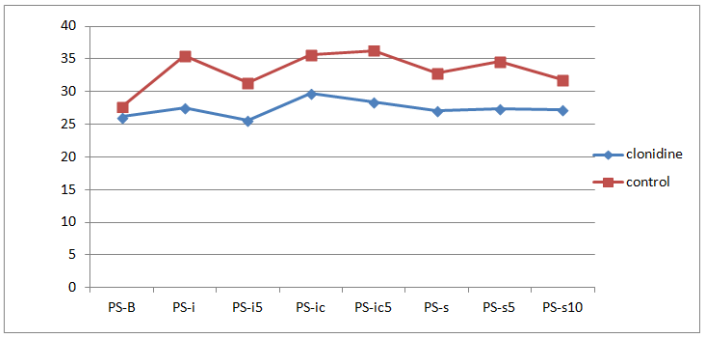
systolic blood pressure (SBP) was monitored and boluses of Inj ephedrine 5mg intravenously were used if MAP fell below 90 mmHg at 2 minutes interval until SBP rose to more than 90 mmHg. The total dose of ephedrine used in each patient was noted. If symptomatic bradycardia occurred inj atropine 0.4mg was given as bolus and noted.Parameters for study were recorded from baseline after insertion of pulmonary artery catheter till 10 minutes after sternotomy.

Statistical Methodology: The data obtained was analysed with the help of Chi square test and Anova test in SPSS software and values obtained within 95%confidence limits (p value less than .05) were considered significant.

Results

The study involved 50 randomized patients with age ranging from 42-70 yrs. The patients in clonidine group had mean age of 56±7 yrs and control group had mean age of 58±9 yrs. The mean Weight and Height of patients in clonidine group was 57±11 kg & 162±11cm and those of control group was 61±8 kg & 164±7 cm respectively.Most significant results were seen in pulmonary circulation. Pulmonary systolic pressures remained 16-28% lower in clonidine group than in control group as shown in Figure 1, while the mean and diastolic pressure were lower by 16-34% and 8-40% respectively as shown in figures 2 and 3.

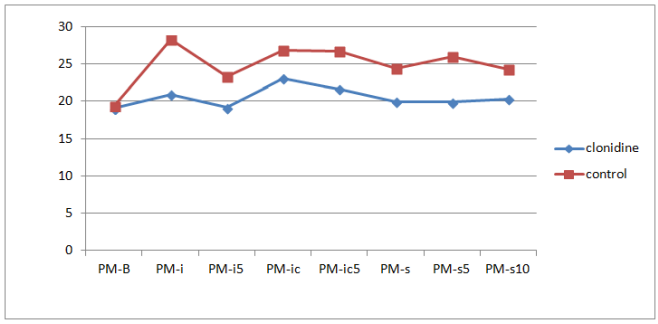
Figure 1: Comparison of Pulmonary Arterial Systolic Pressures



pa sys	B	I	i5	ic	ic5	s	s5	s10
clonidine	26.12±7.6	27.56±9.78	25.56±6.3	29.68±8.67	28.44±6.21	27.12±7.92	27.44±8.84	27.28±7.37
control	27.64±6.24	35.48±8.03	31.32±9.62	35.64±6.66	36.28±7.62	32.8±8.09	34.64±10.89	31.8±6.48
p	0.44	0.002	0.015	0.001	0.001	0.016	0.013	0.026

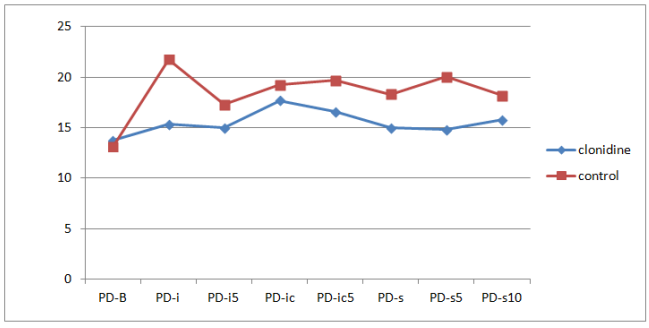
B = baseline, I = induction, i5= 5 min after induction, ic =incision, ic5 = 5 min after incision, s = sternotomy, s5 / s10= 5 /10 min after sternotomy

Figure 2: Comparison of Pulmonary Arterial Mean Pressures



pa mean	B	I	i5	ic	ic5	s	s5	s10
clonidine	19.04±5.98	20.92±7.04	19.16±4.7	23.04±7.33	21.64±5.33	19.92±6.26	19.88±7.1	20.28±5.57
control	19.36±4.43	28.24±8.18	23.36±6.87	26.84±4.89	26.68±5.68	24.44±6.56	26±9.46	24.32±5.07
p	0.83	0.001	0.015	0.036	0.002	0.016	0.013	0.01

Figure 3: Comparison of Pulmonary Arterial Diastolic Pressures.



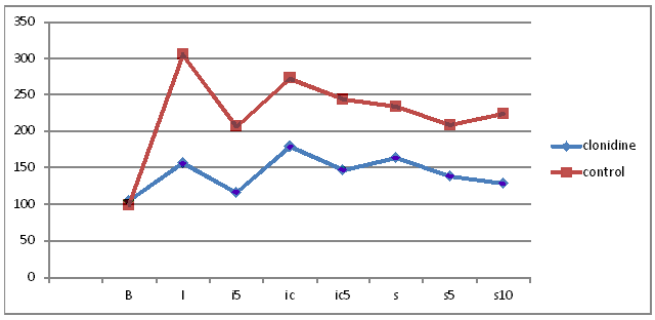
pa dia	B	I	i5	ic	ic5	s	s5	s10
clonidine	13.72±4.5	15.36±5.48	14.96±3.94	17.68±5.73	16.6±4.99	15±5.45	14.84±6.53	15.8±5.12
control	13.12±3.83	21.76±8.51	17.32±4.71	19.24±4.19	19.68±4.93	18.32±6.31	20.04±8.9	18.2±4.96
p	0.614	0.002	0.06	0.27	0.033	0.05	0.02	0.098

B = baseline, I = induction, i5= 5 min after induction, ic =incision, ic5 = 5 min after incision, s = sternotomy, s5 / s10= 5 /10 min after sternotomy.

The pulmonary vascular resistance was lower by 35-70% in clonidine group than in control group

throughout the study period as shown in figure 4. The results in these variables were statistically significant.

Figure 4: Comparison of Pulmonary Vascular Resistance.



pvr	B	I	i5	ic	ic5	s	s5	s10
clonidine	105±59.06	155.82±101.66	116.03±51.86	178.7±160.04	146.35±68.86	163.12±79.02	137.7±74.37	127.74±56.8
control	99.07±59.8	305.82±127.15	206.1±96.32	272.96±126.52	243.33±88.18	233.27±84.29	208.56±76.13	223.55±82.95
p	0.72	0.001	0.001	0.025	0.001	0.004	0.002	0.001

B = baseline, I = induction, i5= 5 min after induction, ic =incision, ic5 = 5 min after incision, s = sternotomy, s5 / s10 = 5 /10 min after sternotomy

Arterial systolic pressures were lower by 2-10% in clonidine group and the mean & diastolic pressures were lower by 3-12 & 2-6% respectively during most of the study period. However statistical significance could not be established for these variables.

Similarly, systemic vascular resistance was lower by 3-25% but results were nonsignificant. Cardiac output was higher in clonidine group by 3-13% however statistical significance could not be established in this case also.

A reduction in heart rate as expected with clonidine was not seen as it was variably higher in both groups at different time periods in our study as shown in figure 5.

Figure 5: Comparison of Heart Rate in the two groups

HR	B	I	i5	ic	ic5	s	s5	s10
clonidine	78.44±12.09	78.04±13.74	67±10.58	78.28±17.06	70.76±9.83	69.16±15.5	69.12±12.7	68.28±10.53
control	71.72±16.42	82.12±16.08	64.96±18.82	79.4±15.02	76.2±12	74.12±20.76	67.44±12.83	71.24±12.33
p	0.14	0.34	0.63	0.80	0.08	0.34	0.64	0.36

B = baseline, I = induction, i5= 5 min after induction, ic =incision, ic5 = 5 min after incision, s = sternotomy, s5 / s10= 5 /10 min after sternotomy

Pulmonary wedge pressure was reduced by 4-26% in clonidine group however statistical significance was not seen. No appreciable trend in CVP measurements was seen.

Discussion

In our study we compared intravenous clonidine 4 µg/kg vs control in patients undergoing coronary artery bypass grafting for reducing the stress response associated with intubation, incision and sternotomy and measured vitals till 10 min after sternotomy. The findings in this study were able to show that clonidine given intravenously at the dose of 4 µg/kg has a very favourable effect on pulmonary circulation as it significantly reduced pulmonary vascular resistance and pulmonary arterial pressures throughout our the study period and thus would help in reduction of cardiac afterload especially on right side and thus help the myocardium in coping with periods of reduced coronary circulation as is usually encountered in patients undergoing cardiac surgery specially coronary artery bypass grafting. Peter j kulka in a randomized double-blind study conducted in 48 coronary artery bypass grafting patients compared 2 ,4 and 6 µg/kg

clonidine and found that clonidine 4 and 6µg/kg significantly reduced hemodynamic and adrenergic reaction to stress, reduced pharmacologic interventions and increased sedation. However, clonidine 6µg/kg was not more effective than 4µg/kg, and clonidine 2µg/kg was equally effective as placebo and thus concluded that clonidine 4µg/kg was the appropriate dose to attenuate the stress response to laryngoscopy in CABG patients[10].

Kahoru nishina et al in a meta-analysis of seven studies published from 1980-1999concluded that perioperative clonidine reduces cardiac ischemic episodes in patients with known or at risk of coronary arterial disease without increasing the risk of bradycardia[11].

M. Zalunardo et al in a study conducted on 33 ASA class I patients scheduled for elective surgery found that clonidine 3µg/kg given as I/V premedication reduces hemodynamic response to tracheal intubation but does not appear to negatively influence cardiovascular stability after intubation. The effects of per orally given clonidine premedication on hemodynamics are less pronounced[12]. However our study did not show any difference in control of tachycardia response during tracheal intubation with the control group as seen in study conducted by M ghignone et al in 30 patients scheduled for elective surgery with a history of arterial hypertension who found that clonidine produced a rapid preoperative control of systolic and diastolic blood pressure and was more effective in blunting the reflex tachycardia associated with laryngoscopy and tracheal intubation than lignocaine – fentanyl pre-treatment. This may have been because most pts in our study were already on beta-blockers and didn't have a significant rise in heart rate during periods of stress.The study also showed a reduction in systemic vascular resistance and systemic arterial pressures. Although the results in these variables were not statistically significant in our study however a positive effect cannot be ruled out as it has been shown in several other studies.

Conclusion

We conclude that clonidine is an effective agent for reducing stress induced increase in intraoperative pulmonary arterial pressure (systolic, diastolic, mean) and pulmonary vascular resistance in cardiac patients which may lead to stable hemodynamics. Clonidine also reduced systemic arterial pressure and pulmonary wedge pressure changes however statistically significant reduction was not seen in our study.

References

1. Cason BA, Demas KA, Mazer CD, Gordon HJ, Hickey RF. Effects of nitrous oxide on coronary pressure and regional contractile function in experimental myocardial ischemia. Anesth Analg. 1991 May;72(5):604 -611.
2. Eger EI 2nd, Lampe GH, Wauk LZ, Whitendale P, Cahalan MK, Donegan JH. Clinical pharmacology of nitrous oxide: an argument for its continued use. Anesth Analg. 1990 Dec;71(6):575-585.
3. Houltz E, Caidahl K, Hellström A, Gustavsson T, Milocco I, Ricksten SE. The effects of nitrous oxide on left ventricular systolic and diastolic performance before and after cardiopulmonary bypass: evaluation by computer-assisted two-dimensional and Doppler echocardiography in patients undergoing coronary artery surgery. Anesth Analg. 1995 Aug;81(2):243 -248.
4. Reiz S, Ostman M. Regional coronary hemodynamics during isoflurane-nitrous oxide anesthesia in patients with ischemic heart disease. Anesth Analg. 1985 Jun;64(6):570 -576
5. Inomata S, Yaguchi Y, Toyooka H. The effects of clonidine premedication on sevoflurane requirements and anesthetic induction time. Anesth Analg. 1999 Jul;89(1):204 -208.
6. Flacke JW, Bloor BC, Flacke WE, Wong D, Dazza S, Stead SW, et al. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary

bypass surgery. Anesthesiology. 1987 Jul;67(1):11 -19
7. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotrachaeal intubation. Anesthesiology. 1986 Jan;64(1):36 -42.
8. Quintin L, Bouilloc X, Butin E, Bayon MC, Brudon JR, Levron JC, et al. Clonidine for major vascular surgery in hypertensive patients : a double-blind, controlled, randomized study. Anesth Analg.1996; 83:687-695
9. Tanaka M, Nishikawa T. Effects of clonidine premedication on the pressor response to alpha-adrenergic agonists. Br J Anaesth. 1995 Nov;75(5):593 -597.
10. Kulka PJ, Tryba M, Zenz M. Dose-response effects of intravenous clonidine on stress response during induction of anesthesia in coronary artery bypass graft patients. Anesth Analg. 1995 Feb;80(2):263 -268.
11. Nishina K, Mikawa K, Uesugi T, Obara H, Maekawa M, Kamae I, et al. Efficacy of clonidine for prevention of perioperative myocardial ischemia: a critical appraisal and meta-analysis of the literature. Anesthesiology. 2002 Feb;96(2):323 -329.
12. Zalunardo MP, Serafino D, Szelloe P, Weisser F, Zollinger A, Seifert B, et al. Preoperative clonidine blunts hyperadrenergic and hyperdynamic responses to prolonged tourniquet pressure during general anesthesia. Anesth Analg. 2002 Mar;94(3):615 -618.
13. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller's anesthesia. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010.
14. Stoelting RK, Gibbs PS. Hemodynamic effects of morphine and morphine-nitrous oxide in valvular heart disease and coronary artery disease. Anesthesiology. 1973 Jan;38(1):45-52.
15. Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A. High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular response. Anesth Analg.1979 Sep-Oct;58(5):390 -395.
16. Moffitt EA, Sethna DH, Gary RJ, Raymond MJ, Matloff JM, Bussell JA. Nitrous oxide added to halothane reduces coronary flow and myocardial oxygen consumption in patients with coronary artery disease. Can Anaesth Soc J. 1983 Jan;30(1):5-9.
17. Moffitt EA, Scovil JE, Barker RA, Imrie DD, Glenn JJ, Cousins CL, et al. The effects of nitrous oxide on myocardial metabolism and hemodynamics during fentanyl or enflurane anesthesia in patients with coronary disease. Anesth Analg. 1984 Dec;63(12):1071 -1075.
18. Davidson JR, Chinyanga HM. Cardiovascular collapse associated with nitrous oxide anaesthetic: a case report. Can Anaesth Soc J. 1982 Sep;29(5):484 -488.
19. 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 choleycystectomy. Acta Anaesthesiol Sin.2000 Mar;38(1):23-29.
20. Joris JL, Chiche JD, Canivet JL, Jacquet NJ, Legros JJ, Lamy ML. Hemodynamic changes induced by laparoscopy and their endocrine correlates: effects of clonidine. J Am Coll Cardiol.1998 Nov;32(5):1389-1396.
21. Hall DL, Tatakis DN, Walters JD, Rezvan E. Oral clonidine pre-treatment and diazepam/ meperidine sedation. J Dent Res. 2006 Sep;85(9):854 -858.
22. Thomson IR, Peterson MD, Hudson RJ. A comparison of clonidine with conventional preanesthetic medication in patients undergoing coronary artery bypass grafting. Anesth Analg. 1998 Aug;87(2):292 -299.
23. Schneemilch CE, Bachmann H, Ulrich A, Elwert R, Halloul Z, Hachenberg T. Clonidine decreases stress response in patients undergoing carotid endarterectomy under regional anesthesia: a prospective, randomized, double-blinded, placebo-controlled study. Anesth Analg. 2006 Aug;103(2):297-302.