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Comparison of oral Clonidine with Nitrous Oxide for balanced anesthesia in cardiac surgeries: a prospective randomized double blind study.

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Abstract

Background: Clonidine, an alfa-2 adrenoreceptor agonist has anaesthetic, analgesic, sedative and sympatholytic properties. Oral clonidine also makes induction of anesthesia faster and smoother when used along with balanced anesthesia technique.

Context: Comparing oral Clonidine with Nitrous Oxide (N_2O) in cardiac surgery cases.

Aim : This study aims to evaluate use of oral Clonidine given prior to surgery and compare with Nitrous Oxides' use in intraoperative period in cardiac surgery cases for hemodynamic effects and overall satisfaction with anesthesia.

Subjects and Methods: In this study 75 patients aged 18-40 yrs posted for cardiac valve repair surgery under cardiopulmonary bypass (CPB) were divided into 3 groups of 25 patients each .Group A (Clonidine) received 150 mcg clonidine tablet preoperatively and no intraoperative N_2O. Group B (Control) received preoperative placebo tablet and no intraoperative N_2O. Group C (N_2O)received oral placebo tablet and intraoperative N_2O. Intraoperative hemodynamics (HR, BP), bispectral index (BIS), MAC for sevoflurane at intubation and at 2,5 and 10 minutes post intubation, and at 2,5 and 10 minutes post sternotomy were noted. Postoperatively patient's awareness under anesthesia and overall satisfaction with anesthesia procedure was enquired and noted.

Results: In our results clonidine was found to be a viable alternative to N_2O as it shortens the anesthesia induction time and decreases overall requirement of volatile inhalational anesthetic agent.

Keywords: Clonidine, Nitrous Oxide, Cardiac surgery, Hemodynamic stress response.

Introduction

At present a combination of anesthetic drugs and gases are used for safe conduct of balanced anesthesia. However, the search for a single ideal, anesthetic agent is always on which can provide all the attributes of anaesthesia safely, smoothly and economically.

N_2O is an integral part of general anesthesia which along with volatile anaesthetic agent provides safe and smooth onset and maintenance of anaesthesia but N_2O is not free from all side effects. It is known to increase mean pulmonary artery pressure and pulmonary vascular resistance while decreasing mean arterial pressure and cardiac index which is highly undesirable in patients with preexisting pulmonary hypertension and right ventricular dysfunction. Hypoxia, hypercarbia, metabolic acidosis and hemodynamic alterations caused by sympathetic response makes the control of pulmonary hypertension even more difficult and can lead to serious complications. So to avoid use of N_2O in general anesthesia an alternative is required.

Clonidine, an alpha-2 adrenoreceptor agonist has anaesthetic, analgesic, sedative and sympatholytic properties. It has been shown to preserve endocardial perfusion and reduce myocardial oxygen demand.

With this background we investigated whether oral clonidine premedication can provide the benefits of N_2O in balanced anesthesia in terms of shortening of induction time, attenuation of stress response to tracheal intubation and decreasing requirement of inhalational anesthetic. Quality of anesthesia in terms of intraoperative awareness and patient satisfaction was also assessed.

Subjects and Methods

This study was conducted after due approval from Institutional Review Board and Hospital ethics committee of Vardhaman Mahavira Medical College and Safdarjang Hospital, New Delhi. It was a prospective, randomized double blind placebo controlled study . Seventy five patients aged 18-40 years posted for elective mitral valve replacement surgery under CPB were enrolled in this study. They were randomly divided into 3 groups according to computer generated randomization technique. Group-A (clonidine group ,n=25) received oral Clonidine and no intraoperative N_2O, Group B (control group ,n=25) received preoperative placebo tablet and no intraoperative N_2O and Group C (N_20 group, n=25)received preoperative placebo tablet and N_2O in intraoperative period.

Patients were kept fasting overnight and were given tablet Alprazolam 0.25 mg orally at night time and 90 minutes prior to surgery. Patients in Group A were given tablet Clonidine 150mcg orally whereas Group B and C patients received vitamin tablets as placebos by different nurses on rotational duties in ICU who were unaware of the study design. Then after 90 minutes, the level of sedation was evaluated using Observer Assessment of Alertness/Sedation scale (OAA/S scale) by different resident anesthesiologist who were also blind to the study. Then the patients were induced for general anesthesia using intravenous morphine 0.1mg/kg,Thiopentone sodium 2-3 mg/kg,Vecuronium Bromide 0.12mg/kg,after cannulating radial artery for invasive blood pressure (IBP) monitoring.Trachea was intubated by direct laryngoscopy with appropriate sized endotracheal tube(ETT). A disposable BIS sensor was also applied on the forehead of the patient. All the vitals viz .ECG, SpO_2, End tidal CO_2 ($EtCO_2$), Systolic BP (SBP), Diastolic BP (DBP), Mean BP, Heart Rate(HR) , and BIS were monitored and recorded intraoperatively. Right internal jugular vein was cannulated for central venous pressure (CVP) monitoring.

For maintenance, Group A and B received no nitrous oxide and only oxygen with sevoflurane was given, whereas Group C received N_2O, oxygen and sevoflurane.Muscle relaxation was maintained using Vecuronium Bromide and analgesia with Injection

Morphine.Concentration of sevoflurane was adjusted to keep BIS at 40 to 50.MeanBP was maintained using Ephedrine bolus,volume or both when required.

Parameters under Study – Time for induction, HR, BP and expiratory MAC of sevoflurane at intubation then at 2,5 and 10 minutes post intubation and also 2, 5, and 10 minutes post sternotomy. All the patients were extubated in ICU after surgery. Patients were assessed 2 hours after extubation and on day 1 post operatively for intraoperative awareness and overall satisfaction in terms of willingness to have same type of anesthesia again in future.

Statistical analysis

ANOVA Test was used for comparison of all the variables in different groups and comparison between groups. ANOVA Test was done by Boforani post hoc.Categorical variables were compared in groups by using chi square/Fischer Exact Test. In the present study $p<0.05$ was considered statistically significant.

Observations and Results

The demographic profile of all the patients was comparable in all the study groups so that the p value was not significant. All the three groups had similar type of surgery ie mitral valve replacement and had almost similar operation times (215-220 minutes). 80-84% of patients in all the groups were having atrial fibrillation therefore almost all the patients were on anti- arrhythmic drugs (digoxin, amiodarone), antihypertensive and diuretics.

Patients in Group A were observed to be calm, sedated and cooperative as compared to Group B and C in which many patients were anxious and complained of pain during venous cannulations . All the three groups had comparable preoperative HR of 93±12.25, 88±13.30 and 91±12.71 respectively (Table1)

Table 1 : Heart Rate

	PRE-OP	ART	INTU	2	5	10	INCISION	STER	2	5	10
GROUP-A	93±12.25	89±10.91	88±11.12	98±11.05	91±8.90	86±8.22	90±7.41	89±8.19	96±7.48	90±6.93	86±7.23
GROUP-B	88±13.30	95±12.56	99±15.06	107±12.76	101±13.34	92±15.33	99±15.06	96±13.31	105±15.45	99±15.53	91±13.43
GROUP-C	91±12.71	97±11.52	90±1O.61	103±6.34	99±13.26	89±13.40	98±13.19	92±14.21	100±15.63	94±16.20	88±13.86

Patients in Group B and C showed rises in HR at arterial line insertion, 2 minutes after intubation , after incision and at 2 minutes post sternotomy while in Group A only latter 3 peaks were there.

In mean SBP , Group A and C showed comparable rises in SBP at 2 minutes post intubation (14.5% rise as compared to preoperative values) whereas Group B showed a rise of 27.9 % which is significant (Table 2)

Table 2: Systolic Blood Pressure

	PRE-OP	ART	INTU	2	5	10	INCISION	STER	2	5	10
GROUP-A	110±8.77	113±10.57	114±10.54	126±12.55	120±12.08	117±11.12	122±11.05	120±8.90	128±8.22	122±7.41	118±8.19
GROUP-B	111±7.52	118±11.70	118±10.14	142±6.4	135±6.27	124±6.55	132±7.60	126±7.62	144±7.22	123±8.86	112±8.57
GROUP-C	114±7.34	121±12.09	115±10.26	131±9.69	121±11.25	112±9.51	117±9.97	116±1.28	128±8.23	119±9.60	114±7.42

Similarly in Diastolic blood pressure (DBP) there was a rise in BP at 2 minutes post intubation of 12.3% and 9.2 % in Group A and C respectively as compared to 21.9 % in Group B (Table 3).

Table 3: Diastolic Blood Pressure

Similar changes were apparent in mean blood pressure (MBP) in Group A and C (Table 4).

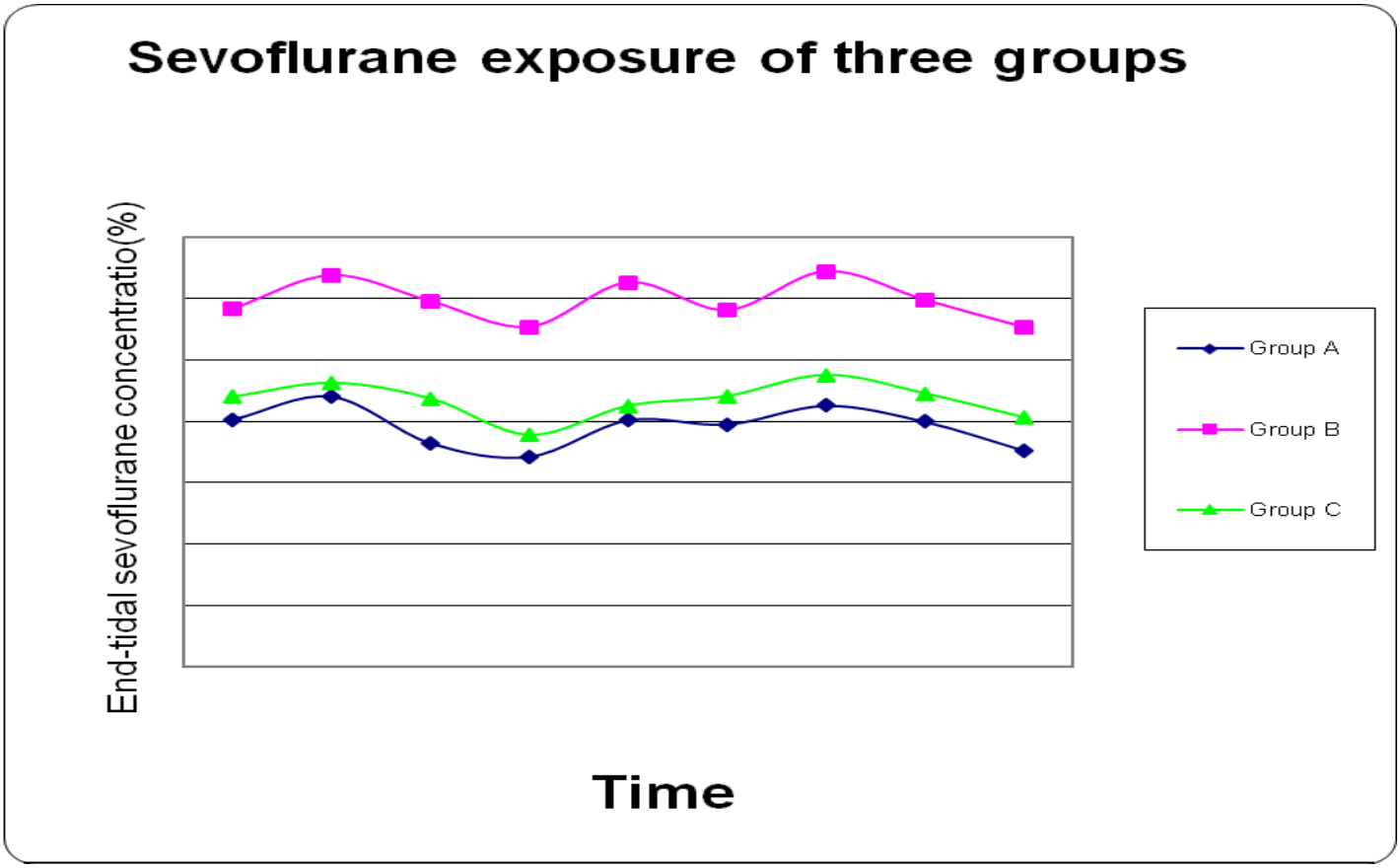
	PRE-OP	ART	INTU	2	5	10	INCISION	STER	2	5	10
GROUP-A	73±6.32	74±7.29	74±5.89	82±6.15	79±6.74	77±10.54	80±12.39	81±12.08	84±10.52	84±11.12	80±8.47
GROUP-B	73±8.9	80±7.85	76±8.97	89±3.62	87±3.61	82±2.46	84±8.10	81±3.60	84±8.10	81±5.97	76±6.19
GROUP-C	76±5.39	79±5.04	78±5.15	83±7.91	80±11.2	76±10.39	78±10.51	79±8.83	82±9.0	80±7.42	78±8.09

Table 4 : Mean Blood Pressure

	PRE-OP	ART	INTU	2	5	10	INCISION	STER	2	5	10
GROUP-A	85±6.9	87±8.14	87±6.73	96±7.79	93±8.07	90±5.89	94±6.13	94±6.74	99±6.86	97±6.15	93±5.26
GROUP-B	86±7.98	93±8.50	90±8.47	106±3.89	103±3.73	96±2.42	100±7.46	96±3.90	104±6.59	95±6.57	88±6.41
GROUP-C	88±5.60	93±6.70	90±6.34	97±13.26	94±10.76	88±9.53	91±9.36	91±8.45	96±9.56	93±7.27	90±6.73

As depicted in Fig 1, significantly more concentration of sevoflurane was needed to keep BIS values within the desirable range in Group B as compared to Group A and C. These were statistically significant. Therefore less sevoflurane was utilized in group A. It was 33% less when compared to Group B and 16.6 % lower than Group C.

Figure 1



As far as the quality of anesthesia and the patient satisfaction was concerned 72% in Group A were very calm preoperatively as compared to 24% in Group B and 20% in Group C. 48% in group A responded positively for a similar anesthesia in future whereas only 24 % wanted the same in group B and C. None of the patients in either group hear or felt any pain intraoperatively.

Discussion

The efficacy of clonidine as a sole premedicant is an established fact as it has sedative and anxiolytic properties [1, 2].Thomas et al [3] in a double blind placebo controlled study reported clonidine to be of overall good quality premedicant. Our results also, indicate that clonidine was very effective in shortening the induction time with thiopentone sodium (Group A=97 seconds, Group B =127 seconds and Group C= 118 Seconds).This is in agreement with a study by Wantanabe T et al [4].

Clonidine blocked the cardiovascular response to laryngoscopy and intubation as it reduces the release of norepinephrine from the nerve endings both centrally and peripherally. In Group A there was a decrease in systolic ,diastolic and mean blood pressure at all the intervals as compared to the preoperative values ($p<0.01$). This result was also consistent with the previous reports{4,5,6].

Many of our patients were on digoxin and amiodarone for control of atrial fibrillation still the increase in HR post intubation in Group A was only 12% as compared

to 22% and 25% in Group B and C respectively ($p<0.01$). Hypotension is also one of the important problems encountered during induction of anesthesia but it was seen that Group A patients responded to lesser pharmacological intervention (ephedrine) whereas other groups required volume infusions too.

Group A patients required lesser doses of sevoflurane to maintain the desired hypnotic levels which is consistent with other studies [4, 7, 8, 9-11]. None of the patients moved or coughed during laryngoscopy and intubation in Group A whereas 20% in Group B and 12% in Group C showed movement /bucking at intubation leading to more episodes of hypertension and tachycardia in these groups.

A higher number of patients selected a similar type of anesthesia in future in Group A as compared to Group B and C. This may be due to the reason that Group A patients were significantly more sedative and calm in the preoperative period allaying operation anxiety.

The patients undergoing CPB are given N_2O for a limited time only i.e. from induction of anesthesia to initiation of bypass. It is not given during bypass or in post bypass period for the risk of air embolism, reperfusion injury, myocardial dysfunction and deleterious effects on the pulmonary arterial pressure. As we have alternative in the form of oral clonidine as proved by this study we can totally avoid N_2O in patients with severe mitral disease with pulmonary hypertension and atrial fibrillation for the want of better hemodynamic control, quicker and smooth induction.

N_2O as reviewed by Robert D Sanders et al [12]in their study - biologic effects of Nitrous Oxide, concluded that it causes a lot of risks like decreasing immunity, hematological toxicity and neurological effects like sub acute combined degeneration of spinal cord[13]. This again strengthens our belief of using alternative drug to N_2O so as to avoid all the complications and side effects attributed to it.

Conclusion

We conclude that Clonidine can be used in place of N_2O in compromised cardiac patients undergoing surgery under cardiopulmonary bypass with safety, economy and better patient comfort and satisfaction.

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