Original Article

Effect of Oral Clonidine Premedication on Perioperative Hemodynamics, Sedation and Analgesia

Sharmin Mahbub[1], Suraya Akter,[2] Ahmed Zahid Al Quadir,[3] Lutful Aziz,[4] Kazi Mesbahuddin Iqbal[5], Azharul Islam[6]

[1]Classified Anaesthesiologist, CMH, Dhaka, [2]Classified Anesthesiologist, CMH, Dhaka, [3]MO, Sylhet MAG Osmani Medical College & Hospital, [4]Consultant, Appollo Hospitals, [5]Ex-Professor, BSSMU, [6]Senior Consultant, Apollo Hospitals.

Abstract

Background: *The current study was designed to investigate the safety and efficacy of oral clonidine as preanesthetic medication on preoperative sedation, analgesia and hemodynamic stability in patients undergoing gynaecological laparotomy.*

Method: *In a prospective, randomized, double-blind, controlled study sixty adult patients of ASA physical status I & II aged 18-40 yrs, undergoing gynaecological laparotomy received placebo (n=30), clonidine 2-2.5mcg/kg (n=30).These drugs were administered 105 min before the estimated time of induction of anesthesia. Heart rate & arterial pressure were recorded prior to induction, 5 min intervally upto 20 min in peroperative time and 2 hour intervally upto6 hours in postoperative period. In the Group-A (clonidine 2-2.5mcg/kg) mean heart rate ranged from73.80±8.69 to 71.45±5.80, while it ranged between 104.40±9.44 to 89.65±5.20 in the Group-B. Systolic blood pressure in Group-A (low dose clonidine) was 113.00±7.32, and in Group-B (placebo) was115.00±5.84 where p=0.024. Diastolic blood pressure of Group-A (low dose clonidine) was 76.15±5.29, and in Group-B (placebo) was 73.65±4.23. Preoperative sleepiness was assessed by both nurse and anesthesiologist and postoperative pain was assessed by a blinded observer using a VAS scale. This study was done in the department of anesthesiology of Apollo Hospitals Dhaka over a period of six months.*

Results: *Patients in group A showed significant hemodynamic changes compared to placebo. Five patients in group A showed marked hypotension and bradycardia and treated accordingly.Group A patients showed sleepiness and post op analgesia compared to group B.*

Conclusion: *These data suggest that clonidine (100mcg/kg) as premedication is effective to produce preop sedation, stable hemodynamics and to facilitate postop analgesia with some side effects.*

Keywords: *Anaesthesia, Premedication, Oral, Hemodynamics, Clonidine*

(JBSA 2019; 32(2): 54-59)

Introduction:

Premedication before anesthesia is considered as an important step in the process of anesthesia. The goals are to produce anxiolysis, analgesia, salivation reduction, to reduce gastric secretion and acidity and to prevent postoperative nausea and vomiting[1] Several drugs are used for premedication such as benzodiazepines, opioid analgesics, butyrophenones, phenothiazines, anticholinergics, â blocker, clonidine & dexmedetomidine etc. Recently different studies found a new and possibly significant role of clonidine in anesthesia and therefore treatment of pain, as the á-2 adrenergic agonist effects produce sedation and analgesia through a central effect and they do not induce respiratory depression[2]. Oral premedication may be advantageous according to the concept of "preemptive analgesia"[2]. Premedication with clonidine produces more satisfactory levels of sedation at induction, decreases emergence agitation and produces more effective early post operative analgesia, when compared with midazolam[1].The purpose of this study is to

determine the safety and effectiveness of oral clonidine premedication in adult patients that is required to produce adequate analgesia and stable hemodynamics.

Materials and Methods:

This prospective, randomized, double-blind comparative study was conducted in the Department of Anaesthesiology of Apollo hospitals Dhaka during the period of July 2012 to December 2012. Prior to the commencement of the study, the research protocol was submitted to the hospital ethics committee &was approved. Study population was the patients, admitted in the department of Gynaecology & Obstetrics. Total 60 randomly selected patients, with the ASA grading I& II, Aged 18-40 years and selected for elective gynaecological laparotomy with a pfannensteil incision were included in this study. On the other hand, Patients taking sedatives, patients taking analgesics, significant neurological or cardiovascular disease,liver or kidney disease,allergy to clonidine,weight heavier than 80 kg, inability to comply with the protocol,i.e, a language barrier, patients had been subjected to gastrointestinal operations(i.e, Billroth 2) patients with a body mass index>35 kg/sq.were excluded. Patients were randomly allocated equally, 30 in each group into two groups, Group-A: clonidine 2-2.5mcg/kg & Group-B: Placebo

Study Procedure:

Data were collected using a structured questionnaire containing all the variables interest. The questionnaire included age, weight, height, ASA grading and the hemodynamic variability of the patients. The hemodynamic variability was assessed by systolic blood pressure, diastolic blood pressure, mean blood pressure and heart rate. All anesthetics were given by the same anaesthesiologists Data recording was performed the night before operation, before administration of test substances on the morning of operation (baseline), at arrival in the operative room (approximately 60 min after premedication) between 90 and 120 min after premedication, at the start of operation, then every 5 min upto 20 min after start of operation, followed by 2 hour intervals upto 6 hr postoperatively. Intraoperative monitoring was consist of electrocardiogram (ECG), automated BP, pulse oximetry(SPO2), and end tidal carbon di oxide and inspired 0xygen concentration. Hypotension was defined as intraprocedural decrease in systolic BP of more than 30% compared with the preinduction level or absolute systolic BP<90 mmHg. Hypertension was defined as an increase in mean arterial BP by more than 15% compared with preinduction values or absolute systolic BP>180 mmHg. Bradycardia was defined as a HR<50 bpm. Bradycardia and hypotension was treated with IV atropine. For postoperative pain control thepatients were given iv pethidine 1 mg/kg as needed in the recovery room. No patient received antiemetic in the postoperative period and also NSAID to assess the pethidine consumption. Analgesia was assessed by nurse by using Visual Analogue Scale in postop room upto 2 hrs.

Statistical Analysis:

Collected data were analyzed using software SPSS program version 18. Frequency distributions of all continuous variables were checked. For analysis of the study results mean, percentage and standard deviation was used. Cross tabulation was prepared. Chi-square, independent t-test, analysis of variance (ANOVA) and correlation were done to see the association. A value of $P<0.05$ has been taken as statistically significant. The graph was made using software Sigma plot 8.0.

Results:

Sixty women were successfully recruited. The patient characteristics are shown in Table-I.Demographic data concerning the patient age, weight, ASA class were comparable among the two groups (Group A,B) (Table I).

No statistically significant difference was found as regard to age, weight, height and ASA class.

Baseline heart rate which was measured in ward shows no significant changes (p=0.773). Heart rate was slower in Group-A (2-2.5mcg/kg clonidine) than Group-B(without clonidine) in preinduction period. Intraoperative heart rate was also slower in Group-A than Group-B. In the Group-A (clonidine 2-2.5mcg/kg) mean heart rate ranged from73.80 ±8.69 to 71.45±5.80 while it ranged between 104.40±9.44 to 89.65±5.20 in the Group-B. In the postoperative period Group-A exhibited

a statistically significant reduction of heart rate variable compared to Group-B.

Baseline systolic blood pressure in Group-A (low dose clonidine) was 113.00±7.32 and in Group-B(placebo) was115.00±5.84 where p=0.024. Preinduction, peroperative and postoperative mean blood pressure was significantly lower at each time interval in the clonidine group than in the placebo group(p=0.001).Hemodynamic changes due to laryngoscopy & intubation exhibited no significant change.

Baseline diastolic blood pressure of Group-A(low dose clonidine) was 76.15±5.29 and in Group-B(placebo) was 73.65±4.23. Mean diastolic pressure before induction, perioperative and in postoperative period showed significant differences (p=0.001) among groups at different follow-up period. Hemodynamic changes due to laryngoscopy and intubation showed significant changes between Group-A and Group-B(p=0.001).

The degree of sedation was not significantly different at baseline. Patients in the Group-A (low dose clonidine) were significantly more sedated compared to the placebo group. In preoperative room significant value observed between groups (p=0.001).

Overall patients satisfaction regarding postoperative analgesia was assessed upto 2 hour by Visual Analogue Scale(VAS).Just after arrival in the postoperative room, there were significant value observed in between groups(p=0.001). After 1 hour Group-A(low dose clonidine) showed less pain than Group-B(placebo). After 2 hours the results are same as before 1 hour value.

Table I *Demographic data of the patients*

	Group –A	Group –B
Age (yr)	24.95 ± 4.62 (18-33)	25.15 ± 3.75 (18-33)
Weight (kg)	66.90 ± 8.56 (55-88)	73.75 ± 10.24 (55-88)
Height (cm)	158.05 ± 4.81 (150-170)	156.75 ± 4.17 (150-162)
ASA I/II	13 / 7	15 / 5

Values are expressed in Mean ± SD, ASA class has been analyzed by Chi-Square test, Analysis of other variables done by One Way ANOVA.

Table II *Heart rate at different follows up period*

Heart rate	Group		p value*
	Group-A	Group-B	
Base line(ward)	75.05±8.28	75.50±3.36	0.773
Preop room	75.25±6.59	83.00±7.46	0.006
Before induction	73.50±6.71	96.65±13.53	0.001
Per operative			
5 minute	73.80±8.69	104.40±9.44	0.001
10 minute	71.75±7.62	99.80±6.46	0.001
15 minute	70.65±7.03	95.40±6.32	0.001
20 minute	71.45± 5.80	89.65±5.20	0.001
Post operative room			
0-2 hours	71.90±5.16	88.25±5.50	0.001
4 hours	72.10±4.32	86.55±2.18	0.001
6 hours	73.90±2.93	85.50±1.93	0.001

Student's T-test was done to analyze the data & data were presented as Mean & ±SD

Table III *Systolic blood pressure at different follows up period*

Systolic BP	Group-A	Group-B	p value*
Base line(ward)	113.00±7.32	115.00±5.84	0.024
Pre op room	117.60±4.47	120.20±7.83	0.001
before induction	111.70±11.39	122.60±2.96	0.001
per operative			
5 minute	102.75±12.81	132.80±4.84	0.001
10 minute	97.30±8.65	128.75±4.51	0.001
15 minute	99.15±7.18	124.95±4.24	0.001
20 minute	99.65±9.33	121.65±4.00	0.001
Post operative room			
0-2 hours	101.55±7.55	122.65±3.31	0.001
4 hours	104.50±6.26	121.50±2.85	0.001
6 hours	108.30±5.75	126.40±3.77	0.001

Student's T-test was done to analyze the data & data were presented as Mean & ±SD

Table IV *Diastolic blood pressure at different follows up period*

Diastolic BP	Group-A	Group-B	p value*
Base line (ward)	76.15±5.29	73.65±4.23	0.001
Pre op room	78.05±5.11	77.10±3.68	0.291
before induction	74.15±5.24	82.80±3.00	0.001
per operative			
5 minute	66.85±8.94	89.85±4.52	0.001
10 minute	61.85±8.78	86.90±1.37	0.001
15 minute	62.20±7.71	83.50±.88	0.001
20 minute	62.75±11.14	79.70±3.93	0.001
Post operative room			
0-2 hours	67.10±3.02	78.90±2.71	0.001
4 hours	68.60±3.43	76.90±3.17	0.001
6 hours	70.35±3.48	82.00±1.94	0.001

Student's T-test was done to analyze the data & data were presented as Mean & ±SD

Table V *Sedation score*

Sedation score in preop room

	Group-A	Group-B	p value*
Anaesthesiologist	2.00±0.00	1.00±0.00	0.001
Nurse	1.95±0.22	1.00±0.00	0.001

Table :Ramsay sedation score

Table VI

Visual analog scale in postop room

	Group		p value*
	Group-A	Group-B	
Just arrival	0.00±0.00	1.20±2.28	0.006
After 1 hour	4.95±1.19	6.75±1.06	0.001
After 2 hour	2.40±.82	3.10±1.20	0.019

Table : Visual analog scale (VAS)

Discussion:

Aim of premedication before anesthesia is to allay anxiety and to facilitate smooth induction by reducing stress response. Clonidine is a noble agent in that sense, because it serves both the purposes. It also reduces amount of anesthetic agents required for surgery. For obvious reasons oral administration is the simplest, cheapest and most readily acceptable way of giving the drug as premedication.

This study shows peroperative heart rate in group-A was stable in comparison to group-B. In postoperative period the result shows the marked hemodynamic stability in group-A upto first four hours in comparison to group-B. After four hours heart rate increases more in group-B (from 69.70±2.07 to 71.20±2.62). In case of group-A heart rate increased from 72.10±4.32 to 73.90±2.93. In group-C we found that patients were relatively tachycardic throughout postop period and heart rate decreased gradually .The effect may be due to postoperative multimodal analgesia.

Our study is comparable with the study of Idit Matot et al [3], they used 300 mcg oral clonidine as premedication to see the effectiveness on the hemodynamic alterations and the incidence of perioperative myocardial ischemic episodes.During the procedure they found significant increase in heart rate of placebo group compared with the baseline and with the clonidine group.

Our study also favors with the study of Matot et al [3]. They evaluated the effects of 300 mcg oral clonidine premedication or placebo on the hemodynamic alterations and found significant increase in blood pressure in patients receieved placebo compared with the baseline and with the clonidine group.

In another study Mikawa et al [4] observed two doses of clonidine to investigate the efficacy as premedicant preceding oral atropine in children. They used clonidine 2mcg/kg and 4mcg/kg orally and found that clonidine attenuated the hemodynamic response after intubation and there were no significant perioperative hypotension and bradycardia. In our study we did not use inj atropine after clonidine premedication but five patients of group-A(clonidine2-2.5mcg/kg) had marked bradycardia and hypotension requiring drug therapy in operating room after induction, whereas none of the group-B had these complications.

Throughout the study period(perioperative) group-A showed significantly stable blood pressure but in group-B the record was significantly varied where just before induction and after 5 min of induction both SBP and DBP was highest in comparison to their baseline blood pressure. In our study we found that systolic blood pressure reduced in group-A than group-B. This study is almost similar to the study of Dipak L Raval and Malini K Mehta [5]. They used clonidine 4mcg/kg (200 mcg) for reduction of hemodynamic response to laryngoscopy and intubation and found significant reduction of mean arterial pressure in clonidine group.

In our study patients group-A and group-B showed clinically significant difference in sleepiness preoperatively which was assessed by both nurse and anesthesiologist. It may be due to decreased anxiety of clonidine groups. In group-B patients were well alert. Hidalgo et al [6] reported that they studied oral clonidine 100 mcg on 29 patients and placebo for another 32 patients. They found significant anxiolysis and analgesia throughout the 72 hr after surgery, although the subjects who receieved clonidine was sleepier than the control group for the first 6 hr after surgery. In another study Filos et al [7] showed that those patients who receieved clonidine 150mcg were significantly more sedated as compared to those given placebo($p<0.01$), where sedation persisted for more than 6 hr postoperatively.

Just after arrival in postop room there were no pain in group-A but in group-B patients showed significant pain (1.20±2.28). After 1 hr VAS score is high in group-B patient (6.75±1.06) but low in group-A (4.95±1.19) and. After 2 hr the values showed no significant change for both groups due to pethidine consumption

Our relatively small sample size may limit the interpretation of our results. Neverthless, the results of the present study should encourage the routine use of clonidine (100 mcg) as premedication for female patients undergoing gynaecological laparotomy. By providing improved hemodynamics, clonidine may benefit a whole range of patients, particularly those with hypertension.

Conclusion

Our study concluded that clonidine provides sleepiness, stable hemodynamics and postoperative analgesia. So, routine use of clonidine as premedication in adult female patients in gynaecological laparotomy cases would be safe & effective and important cardiovascular side effects (notably hypertension and tachycardia) can also be minimized. However further study is recommended to find out its efficacy in patients with compromised cardiovascular system and with a larger sample size.

References:

1. Dhamani S, Brasher C, Goldmard J, et al. Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies .Acta Anaesthesiol Scand 2010;54:397-402.
2. Mikawa K, Maekawa N, Nishina K, et al. Oral clonidine premedication reduces postoperative pain in children. Anesthesia and analgesia 1996 ; 82:225-30.
3. Kumar A, Bose S, Bhattachaey A, et al. Oral clonidine premedication for elderly patients undergoing intraocular surgery. Acta Anaesthesiol Scand 1992;36:159-64
4. Muzi M, Golf D R, Elbart T J, et al. Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. Anesthesiology1992;77:864-871.
5. Steven M Yentis,Nicolas P et al.Anesthesia and intensive care.A-Z.An encyclopedia of Principles and practice.2009;Page443
6. Hackmann T , Allen S, Friesen M, et al . Clonidine facilitates controlled hypotension in adolescent children. Anesthesia Analgesia 2003;96:976-81.
7. Higuchi H, Adachi Y, Dahan A, Olofsen E, et al. The interaction between propofol and clonidine for loss of consciousness. International anesthesia research society 2002;94:886-91