Original Article

A Dose Response Study Of Oral clonidine as premedication in patients undergoing abdominal gynaecological surgery

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Abstract

Background: *The current study was designed to investigate the safe and effective dose of oral clonidine on post-operative analgesia in patients undergoing gynaecological laparotomy. The objective of the study was to see the effectiveness of oral Clonidine as a preanesthetic medication and to determine which dose of oral Clonidine gives better analgesic effect.*

Method: *In this prospective, randomized, double-blind, controlled study sixty adult female patients of ASA physical status I & II aged 18-40 yrs, undergoing gynaecological laparotomy received low dose clonidine 2-2.5mcg/kg (n=30) and high dose clonidine 4-4.5mcg/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 upto 6 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, in Group-B mean heart rate decreased more from 70.85±7.64 to 67.85±6.47. Systolic blood pressure in Group-A (low dose clonidine) was 113.00±7.32, in Group-B (high dose clonidine) was 120.00±10.38 and where p=0.024. Diastolic blood pressure of Group-A (low dose clonidine) was 76.15±5.29, in Group-B(high dose clonidine) was 80.10±5.3. 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 (low dose) and group B (high dose) showed no significant hemodynamic changes between groups. Five patients in group B showed marked hypotension and bradycardia and treated accordingly.Group B patients (high dose clonidine) showed more post operative analgesia compared to group A.*

Conclusion: *These data suggest that low dose clonidine (100mcg/kg) premedication is safe and effective to facilitate post-operative analgesia with stable haemodynamics & without any side effects. On the other hand,.high dose clonidine showed more post op analgesia &.marked hypotension and bradycardia*

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

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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 laqnguage 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:*** clonidine 4-4.5mcg/kg.

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 the patients 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-1. Demographic data concerning the patient age, weight, ASA class were comparable among the two groups (Group A,B) . 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)(Table-II). Heart rate was slower in Group-A (2-2.5mcg/kg clonidine) than in Group-B(4-4.5mcg/kgclonidine) in preinduction period. Intraoperative heart rate was also slower in Group-B than Group-A. In the Group-A (clonidine 2-2.5mcg/kg) mean heart rate ranged from73.80 ±8.69 to 71.45±5.80, in Group-B mean heart rate decreased more from 70.85±7.64 to 67.85±6.47, In the postoperative period Group-B exhibited a statistically significant reduction of heart rate variable compared to Group-A.

Baseline systolic blood pressure in Group-A (low dose clonidine) was 113.00±7.32, in Group-B (high dose clonidine) was 120.00±10.38 and preinduction, peroperative and postoperative mean blood pressure was significantly lower at each time interval in the clonidine group.Hemodynamic changes due to laryngoscopy & intubation exhibited no significant change(Table-III).

Baseline diastolic blood pressure (Table-IV) of Group-A (low dose clonidine) was 76.15±5.29, in Group-B(high dose clonidine) was 80.10±5.3. 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 no significant changes between Group-A and Group-B(p=0.691).

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=0.006). After 1 hour Group-B(high dose clonidine) showed less pain than Group-A(low dose clonidine) . After 2 hours the results are same as before 1 hour value.

Table 1 Demographic data of the patients

	Group –A	Group –B
Age (yr)	24.95 ± 4.62 (18-33)	25.15 ± 4.25 (18-34)
Weight (kg)	66.90 ± 8.56 (55-88)	71.00 ± 7.51 (60-88)
Height (cm)	158.05 ± 4.81 (150-170)	154.75 ± 3.94 (150-162)
ASA I/II	13 / 7	11 / 9

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

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	76.55±7.57	0.773
Preop room	75.25±6.59	74.85±11.36	0.006
Before induction	73.50±6.71	71.95±9.19	0.001
Per operative			
5 minute	73.80±8.69	70.85±7.64	0.001
10 minute	71.75±7.62	67.90±7.48	0.001
15 minute	70.65±7.03	68.85±6.93	0.001
20 minute	71.45± 5.80	67.85± 6.47	0.001
Post operative room			
0-2 hours	71.90±5.16	69.60±4.61	0.001
4 hours	72.10±4.32	69.70±2.07	0.001
6 hours	73.90±2.93	71.20±2.62	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		P value
	Group-A	Group-B	
Base line(ward)	113.00±7.32	120.0±10.38	0.024
Pre op room	117.60±4.47	122.05±12.37	0.001
before induction	111.70±11.39	106.60±12.67	0.001
per operative			
5 minute	102.75±12.81	100.05±10.05	0.001
10 minute	97.30±8.65	99.10±10.77	0.001
15 minute	99.15±7.18	98.20±9.89	0.001
20 minute	99.65±9.33	95.25±7.318	0.001
Post operative room			
0-2 hours	101.55±7.55	99.55±6.05	0.001
4 hours	104.50±6.26	101.10±7.52	0.001
6 hours	108.30±5.75	108.30±5.75	0.001

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

Table IV: Diastolic blood pressure at different follows up period

Diastolic BP	Group		p value*
	Group-A	Group-B	
Base line (ward)	76.15±5.29	80.10±5.30	0.001
Pre op room	78.05±5.11	80.00±8.01	0.291
before induction	74.15±5.24	69.45±8.33	0.001
per operative			
5 minute	66.85±8.94	65.90±5.66	0.001
10 minute	61.85±8.78	65.90±7.71	0.001
15 minute	62.20±7.71	64.75±7.87	0.001
20 minute	62.75±11.14	64.70±6.43	0.001
Post operative room			
0-2 hours	67.10±3.02	65.10±7.55	0.001
4 hours	68.60±3.43	67.40±4.39	0.001
6 hours	70.35±3.48	70.00±4.20	0.001

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

Table V: Visual analog scale (VAS)

Visual analog scale in postop room	Group		p value*
	Group-A	Group-B	
Just arrival	0.00±0.00	0.00±0.00	0.006
After 1 hour	4.95±1.19	3.30±.97	0.001
After 2 hour	2.40±.82	2.30±.73	0.019

Discussion:

Aim of premedication before anesthesia is to allay anxiety and to facilitate smooth induction by reducing stress response. Clonidine serves both the purposes. So, clonidine may be the simplest, cheapest and most readily acceptable 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 greatest hemodynamic stability in group-B upto first four hours in comparison to group-A. 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. Our study is also comparable with the study of Filos.S.K..,Patroni.O.,Goudas.C.L.,(1993)[4]. They studied clonidine on two groups, one group receieved 150mcg Clonidine (2-2.5mcg/kg) and another group receieved 300mcg Clonidine (4-4.5mcg/kg). They also found significant reduction in mean arterial pressure which was more pronounced and occured earlier after 300mcg clonidine as compared to 150 mcg of clonidine. This result favors with the result of our study. Our study is comparable with the study of Idit Matot et al [5], 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.

In another study Mikawa et al[3] 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 nine patients of group-B(clonidine4-4.5mcg/kg) had marked bradycardia and hypotension requiring drug therapy in operating room after induction, whereas none of the group-A . In our study we found that systolic blood pressure reduced more in group-B than group-A. This study is almost similar to the study of Dipak L Raval and Malini K Mehta [6]. 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 we found that systolic blood pressure reduced more in group-B than group-A. At the higher dose there is chance of hypotension which is less in lower dose of clonidine. In our study patients group-A and group-B showed no clinically significant difference in sleepiness preoperatively. Hidalgo et al [7] 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. Just after arrival in postop room there were no pain in group-A and group-B patients.

Our relatively small sample size may limit the interpretation of our results. Nevertheless, the results of the present study should encourage the routine use of low dose 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 after induction and throughout the procedure high dose clonidine is associated with more postoperative analgesia than low dose clonidine but it produced much more hypotension and bradycardia in comparison to low dose clonidine group.

Recommendation

We believe that 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.

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