ORIGINAL ARTICLE

Oral Clonidine as Pre-Medication on Perioperative Haemodynamics, Sedation and Analgesia

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Abstract

Background: The current study was designed to investigate the efficacy of oral clonidine as pre-anesthetic medication on preoperative sedation, analgesia and hemodynamic stability in patients undergoing gynecological laparotomy.

Methods: It was a prospective, randomized, double-blind, controlled trial conducted on sixty adult female patients of ASA physical status I and II, aged 18-40 years, undergoing gynecological laparotomy. Patients were randomized to receive either oral clonidine 2-2.5mcg/kg (30 patients) or placebo (30 patients). Endpoints of the study were hemodynamic status (measured as heart rate and blood pressure), level of sedation (measured by the Ramsay sedation score) and level of analgesia (measured as VAS score). Comparison of both groups was done by independent t-test or chi-square test as required.

Results: Hemodynamic status was more stable in clonidine group. Fluctuation of heart rate and per-operative hypertension was less frequent in patients receiving clonidine compared to placebo. Moreover, clonidine showed better efficacy in preoperative sedation and postoperative analgesia compared to placebo (Ramsay sedation score was 2.0 vs 1.0 and VAS score was 4.9 vs 6.7 in clonidine group and placebo group respectively).

Conclusion: Our findings suggest that oral clonidine (2-2.5mcg/kg) as pre-anesthetic medication is effective to produce pre-operative sedation, stable hemodynamics and to facilitate postoperative analgesia in elective gynecological laparotomy cases.

Keywords: Clonidine, Premedication, Anesthesia, Hemodynamics, Analgesia

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Introduction

Anesthetic hazard is a major challenge for successful postoperative outcome[1]. A wide range of pharmacological and nonpharmacological measures are practiced to mitigate this hazard. Premedication before anesthesia is considered as an important step in the process of safe anesthesia. The goals are anxiolysis, analgesia, hemodynamic management, reduction of salivation, reduction of gastric secretion and acidity and prevention of postoperative nausea and vomiting[2]. Several drugs are being used for premedication such as benzodiazepines, opioid analgesics, butyrophenones, phenothiazines, anticholinergics, β blocker, clonidine and dexmedetomidine etc.[3]

Per-operative induced hypotension is practiced since long for many major surgeries as it reduces possibility of bleeding and contributes to decreased surgical time, better visualization of the surgical field, and increased quality of the surgery. However, this procedure may have some disadvantages, such as impairment of perfusion of vital organs[4]. Hence, maintenance of optimum hemodynamic state is crucial for successful anesthesia. On the other hand, postoperative pain management plays an important role in early mobilization and wellbeing of surgical patients. Postoperative pain mostly generates from peripheral tissue injury, which provokes peripheral sensitization and leads to central sensitization. It is a direct consequence of tissue trauma and inflammation. Tissue trauma leads to the release of wide range of inflammatory mediators like bradykinin, serotonin, histamine, and cytokines that act synergistically to convert high threshold nociceptors to low-threshold nociceptors and induce postoperative pain[5].

Clonidine, a promising α-2 agonist, has successfully been used in producing preoperative sedation[6], increased perioperative hemodynamic stability[7,8], and reduced requirements of volatile anesthetic agents[9]. Moreover, it has an analgesic effect by enhancing the effect of both central and peripheral nerve blocks[10]. In Bangladesh, the hemodynamic and analgesic effect of clonidine was explored in some previous studies for different surgeries[11,12]. However, its effect was not explored in case of gynecological laparotomy. Hence the objective of the present study was to determine the efficacy of oral clonidine premedication on perioperative hemodynamics, sedation and analgesia.

Methods

Study design and setting

This was a prospective, double-blind, randomized controlled trial conducted in the Department of Anesthesiology of Apollo hospitals Dhaka during the period of July 2012 to December 2012.

Patients

The patients admitted in the department of Gynecology and Obstetrics for elective gynecological surgery were enrolled in this study. Inclusion criteria were: aged between 18 and 40 years, ASA grading I and II, and selected for elective gynecological laparotomy with a pfannensteil incision. Patients taking sedatives, analgesics, patients with significant neurological or cardiovascular disease, liver or kidney disease, allergy to clonidine, weight heavier than 80 kg and/or a body mass index>35 kg/m^2, inability to comply with the protocol, i.e, a language barrier, subjected to gastrointestinal operations (i.e, Billroth 2) were excluded. According to these criteria a total of 60 patients were recruited after obtaining informed written consent and randomized into two groups by coin toss method. Both the patients and anesthesiologists were blind about the intervention.

Intervention

Patients were equally randomized into two groups to receive either oral clonidine 2-2.5mcg/kg (30 patients) or placebo (30 patients).

Endpoints

Hemodynamic status (measured as heart rate and blood pressure), level of sedation (measured by the Ramsay sedation score) and level of analgesia (measured as VAS score) were the primary endpoints of the study.

Data collection procedure

Data were collected using a structured questionnaire containing all the variables of 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 anesthesiologists. 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 up to 20 min after start of operation, followed by 2 hour intervals up to 6 hour postoperatively. Intraoperative monitoring was consist of electrocardiogram (ECG), automated BP, pulse oximetry (SPO2), and end tidal carbon dioxide and inspired oxygen concentration. Hypotension was defined as intra-procedural decrease in systolic BP of more than 30% compared with the pre-induction level or absolute systolic BP<90 mmHg. Hypertension was defined as an increase in mean arterial BP by more than 15% compared with pre-induction 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 postoperative room up to 2 hrs.

Collected data were analyzed using SPSS version 18.0. Frequency of distributions of all continuous variables were checked. For analysis of the study results mean, percentage and standard deviation were used. 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.

Results

Average age (SD) of the clonidine group was 24.9 (4.6) years and of the placebo group was 25.1 (3.7) years which was similar in both groups. Moreover, other demographic variables like height, weight and ASA grade was also similar in both groups **(Table I)**.

Table I: Sociodemographic characteristics of the patients (n=60)

Characteristics	Clonidine, Mean ± SD (Range)	Placebo, Mean ± SD (Range)	P value
Age (year)	24.95 ± 4.62 (18-33)	25.15 ± 3.75 (18-33)	0.152
Weight (kg)	66.90 ± 8.56 (55-88)	73.75 ± 10.24 (55-88)	0.063
Height (cm)	158.05 ± 4.81 (150-170)	156.75 ± 4.17 (150-162)	0.326
ASA I/II (%)	13 / 7	15 / 5	0.690

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

At baseline, average heart rate of both groups was similar (75 beats per minute in clonidine group and 75.5 beats per minute in placebo group). However, at preoperative room, during operation as well as at postoperative room heart rate was lower and close to baseline in clonidine group while increased in the placebo group. Similar trend was observed in case of blood pressure. Induced hypotension was adequately achieved and maintained in clonidine group while both systolic and diastolic blood pressure in placebo group was higher in placebo group **(Table II)**. A total of five patients of this group had marked bradycardia and hypotension requiring drug therapy in operating room after induction.

Table II: Hemodynamic status of the patients

Parameters	Clonidine, Mean ± SD	Placebo, Mean ± SD	p value
Heart rate			
Base line(ward)	75.05±8.28	75.50±3.36	0.773
Preoperative 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
Postoperative 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
Systolic BP			
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
Postoperative 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
Diastolic BP			
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
Postoperative 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

Values are expressed in Mean ± SD, analysis of other variables done by t-test

In case of preoperative sedation, clonidine was more efficacious compared to placebo (Ramsay sedation score was 2.0 in clonidine group and 1.0 in placebo group) **(Table III)**. Moreover, postoperative pain was better managed in clonidine group compared to placebo group (VAS score was 4.9 after one hour and 2.4 after two hour in clonidine group and 6.7 after one hour and 3.1 after two hour in placebo group) **(Table IV).**

Table III: Postoperative sedation score of the patients

Sedation score in pre op room	*Clonidine, Mean ± SD*	Placebo, Mean ± SD	p value
Anesthesiologist	2.00±0.00	1.00±0.00	0.001
Nurse	1.95±0.22	1.00±0.00	0.001

Values are expressed in Mean ± SD, analysis of other variables done by t-test

Table IV: Visual analogue scale of pain score in patients (n=60)

VAS score in postop room	Clonidine, Mean ± SD	Placebo, Mean ± SD	p value
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

Values are expressed in Mean ± SD, analysis of other variables done by t-test

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.

Our study evidenced that per-operative heart rate in clonidine group was stable in comparison to placebo group. Also in postoperative period the result showed marked hemodynamic stability in clonidine group up to first four hour in comparison to placebo group. After four hours heart rate increased more in placebo group. In placebo group, patients had tachycardia throughout postoperative period and then heart rate decreased gradually. The effect may be due to postoperative multimodal analgesia. Our findings are comparable with some previous studies where use of oral clonidine as premedication decreased the hemodynamic alterations and the incidence of perioperative myocardial ischemic episodes[8,13–15]. Besides, our findings support that clonidine has better efficacy in achieving induced hypotension during surgery compared to placebo. We found significant increase in per-operative blood pressure in patients

who received placebo compared with the patients who received clonidine. These findings supports some previous trials with clonidine as pre-anesthetic medication those evidenced that clonidine reduces rate of per-operative hypertension and favors hemodynamic stability[7,8]. In a study conducted by Mikawa et al. found that clonidine attenuated the hemodynamic response after intubation and there were no significant perioperative hypotension and bradycardia[16]. However, in our study we did not use atropine after clonidine premedication and five patients of this group had marked bradycardia and hypotension requiring drug therapy in operating room after induction, whereas none of the placebo had these complications.

In our study, patients of clonidine group and placebo group showed statistically significant difference in sleepiness preoperatively which was assessed by both nurse and anesthesiologist. It may be due to decreased anxiety of the clonidine group. In placebo group patients were well alert. It was also evidenced in some previous studies where clonidine showed better sedative efficacy compared to placebo as well as other medications like midazolam[6,17]. Besides sedation, we observed a better analgesic effect of clonidine compared to placebo. On arrival to the postoperative room the patients receiving clonidine reported no pain and after one hour they reported less pain compared to the patients who received placebo. However, after 2 hours of surgery pain level showed no significant difference in both groups due to pethidine consumption. Use of clonidine as oral premedication before surgery led to an early onset of sensory block, with prolonged duration of sensory and motor blocks and also decreases analgesic requirement over the next 24 hours, even more efficacy was demonstrated by clonidine compared to etoricoxib and gabapentin[10].

Limitations

Our study has several limitations. Firstly the sample size was small and selective to the female patients requiring elective gynecological laparotomy; hence the findings might not be inferential for all other surgeries. Detailed clinical condition of the patients was not presented in the present study which might limit the generalizability of the findings. Moreover, comparison with other available options for pre-anesthetic medication was not done in the present study.

Conclusion

Our study concluded that clonidine provides stable hemodynamics, adequate sedation and postoperative analgesia in patients requiring elective gynecological laparotomy. So, routine use of clonidine as premedication in adult female patients would be safe and 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.

Declaration

Ethics approval:
Ethical approval was taken from the Institutional Review Board of Apollo Hospitals Dhaka.

Author contributions:
Conception and development of the idea *SM, SA*
Data collection *AZAI, SM, SA*
Data analysis *LA, SM*
Writing - Original Draft Preparation *SM, LA*
Writing – Review & Editing *KMI, AI*

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