2017

Use of Clonidine in Sedation Dentistry

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Use of Clonidine in Sedation Dentistry

CAPSTONE PROJECT PAPER

A paper submitted in partial fulfillment of the requirements for the degree of
Masters of Public Health
in the
University of Kentucky College of Public Health

By
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Lexington, Kentucky
November 15, 2017

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Abstract

Background:

Clonidine is an alpha-2 adrenergic agonist which has been used to treat hypertension for over 40 years. In October 2008, clonidine was approved by the FDA for use as a premedication agent prior to sedation. The overall goal of this study is to determine if clonidine can be used as a pre-operative sedative agent in moderate sedation dentistry and if so, what should be considered a safe level.

The following specific aims were established for this study:

1. To determine whether patients receiving clonidine required less intravenous medications.
2. To determine if clonidine can lower blood pressure and pulse to a safe level (allowing adequate perfusion).
3. To assess whether larger doses of oral clonidine 0.2 mg are significantly different in lowering blood pressure and pulse from lower doses of 0.1 mg.

Methods:

This study was a clinical, cross sectional study of patients in a major inner city dental clinic that provides free dental care to patients in financial need. Data were collected from treatment records completed from March 2012-April 2012. The associations between study sample characteristics and use of clonidine at two dose levels (0.1 mg and 0.2 mg vs. controls) were examined. An analysis of variance was undertaken with the Duncan's Multiple Range Test for comparison of the hemodynamic changes (e.g. systolic, diastolic, mean arterial pressure, and pulse) of patients taking clonidine 0.1 mg, clonidine 0.2mg, and the control group.

Results:

At pre-sedation, the clonidine 0.2 mg group had lower systolic and diastolic blood pressures than the 0.1 mg group and the control group. During first intraoperative period, the results show the mean systolic blood pressure of 0.2 group was significantly lower than the control group. After adjustment for age, BMI, and dose of Versed administered, mean systolic blood pressures for the 0.2 mg clonidine dose group were significantly lower at pre- sedation and the

first intraoperative times in comparison to the 0.1 mg group and the controls. Diastolic blood pressures were not different by the three groups after adjustment in the model. The use of clonidine at both dose groups did not significantly change the amount of sedation medication required, although the data did suggest more sedatives were required at lower clonidine doses.

Conclusion:

This study did not find that the use of clonidine led to a significant reduction in the amount of sedation medication needed. The mean systolic blood pressures for the 0.2 mg clonidine dose group were significantly lower at pre- sedation and the first intraoperative times in comparison to the 0.1 mg group and the controls in the adjusted model; however, there were no significant differences across the measurement times for the effect of clonidine on diastolic blood pressure. Further research with a more robust sample size in the dose groups and improved clinical trial design characteristics would improve our assessment of the effectiveness of the use of clonidine in sedation dentistry.

Introduction

In dentistry, benzodiazepines are the most common sedatives used to relieve anxiety either alone or prior to venous cannulation for moderate sedation (1). There are a variety of choices of benzodiazepines including: diazepam, triazolam, midazolam, and lorazepam (1). Also, there are other types of drugs for preoperative dental sedation including GABA agonists (zolpidem, zaleplon) and antihistamines (hydroxyzine, diahydramine) (1).

The most commonly used benzodiazepine in dental practice is triazolam (Halocin) (2). Triazolam has safety advantages, such as a relatively short-acting, sedative affect, but it may temporarily cause amnesia (but not in doses 0.5 mg or under) (3, 4). On the negative side and like other benzodiazepines, triazolam causes relaxation of muscles that support the airway which can cause respiratory depression that leads to upper airway obstruction (5). Moreover, triazolam causes high blood pressure and tachycardia, indicating patients are in a high adrenergic state despite having taken an oral sedative (5).

Clonidine is an alpha-2 adrenergic agonist which has been used to treat hypertension for over 40 years (6). In October (2008), the FDA approved clonidine for use as a premedication agent prior to sedation (7). Clonidine reduces anesthetic requirements, reduces post-operative shivering, and may reduce post-operative nausea and vomiting (8). Additionally, clonidine has a sympatholytic effect, post-operative analgesia, and does not cause respiratory depression unless there is overdosing (9). Moreover, clonidine doesn't cause amnesia (9).

The overall goal of this study is to determine if clonidine can be used as a pre-operative sedative agent in moderate sedation dentistry and if so, what should be considered a safe level.

This study examines clonidine as a pre-op-sedative agent to accomplish these specific aims:

1. To determine whether patients receiving clonidine required less intravenous medications.
2. To determine if clonidine can lower blood pressure and pulse to a safe level (allowing adequate perfusion).

3. To assess whether larger doses of oral clonidine 0.2 mg are significantly different in lowering blood pressure and pulse from lower doses of 0.1 mg.

Literature review

The literature review is the summary of studies which were done for examining the advantages of clonidine as pre-op-medication in medicine and dentistry. The literature review was collected from PubMed using the terms *clonidine in dentistry* and *clonidine as a pre-sedative agent*.

Around 1995, clonidine began being reported in dentistry as an oral premedication prior to intravenous sedation (13,14,15). Most of these early studies were done outside of The United States. In Japan (1995), Murai and colleagues **(**13) performed a single-blind cross over study on eight healthy adults with intravenous sedation performed twice on each subject (surgical extraction of third molars on both sides). In the clonidine-treated group, the subjects were given about 5 micrograms (mcg) per kilogram (kg) (0.35mg for a 70 kg person) of oral clonidine every 2 hours before the initiation of intravenous sedation with midazolam. In the control group, midazolam was given alone. The parameters measured were dose of midazolam, change in vital signs, recovery time, amnesia and side effects. It was found that oral clonidine given pre-operatively could reduce the dose of intravenous (IV) midazolam by an average of 45%; the documented recovery time was notably shorter than the control group as well.

In Italy (1998), Fanini and colleagues (14) used 150 micrograms (0.15 mg) of oral clonidine (n=20) or placebo 90 minutes prior to conducting conservative, prosthetic or dental

surgery procedures. A blinded observer recorded salivary flow and blood pressure every 30 minutes over 2-3 hours, as well as the degree of pain and sedation occurring intra- and post-operatively. Results of this study found that clonidine produced significant sedation ($p<0.001$), salivary flow reduction ($p<0.001$), and lower post-operative pain scores ($p<0.05$). After taking clonidine, the systolic blood pressure of the patients decreased significantly, but none required treatment for hypotension. Of the patients who received clonidine, 55% positively evaluated the experience.

In a more recent review of clonidine's use as an oral premedication in dentistry (2005), Mutzbauer and Obwegeser (15) suggested that premedication with clonidine blunts the stress response to surgical stimuli and also that the narcotic and anesthetic dose can be reduced. Furthermore, preoperative myocardial ischemic events can be prevented by application of clonidine. Mutzbauer and Obwegeser found that oral clonidine at a dose of 1.5-2.0 mcg/kg (0.105 mg - 0.140 mg in a 70kg person) combines the advantages of benzodiazepines and morphine: anxiolysis, sedation and analgesia with stable hemodynamic, and respiration. However, clonidine does not have the morphine-related side effects such as nausea and vomiting. Although doses of up to 5 mcg/kg (0.35 mg for a 70kg person) have been used in young, healthy patients preoperatively in dental and maxillofacial surgery without significant side effects, it appears that clonidine at 2 mcg/kg (0.140 mg in a 70 kg person) should be an adequate oral premedication dose for these patients when the procedure is performed under local anesthesia in the ambulatory setting. Other recommendations were that clonidine at 2mcg/kg (0.140 mg in a 70 kg person), should not be exceeded in elderly patients to avoid excessive hypotension and sedation. Finally, it was noted that bradycardia is a contraindication of clonidine.

In a 2006 study by Hall and colleagues (16), oral clonidine was prescribed as a pre-sedative (0.1 mg/35kg or 0.2 mg in a 70 kg person) in a randomized, crossover, placebo controlled clinical trial with 13 participants. The purpose of this study was to characterize the

effects of consuming oral clonidine before IV diazepam/meperidine sedation using the bi-spectral index (BIS). BIS is one of several technologies used to monitor depth of anesthesia.

Typically, depending on the sedation agents used, drugs are titrated to a pre-determined BIS value (endpoint) and used to maintain that BIS reading throughout the procedure. However, in moderate (IV or conscious) sedation, attempting to titrate drugs this way can result in over-dosage, but use of BIS can act as an effective alarm warning of over sedation. For moderate sedation monitoring, BIS alarms can be set at a value of 70-75. In this study, clonidine significantly increased the numbers of BIS-depressed readings and percent memory loss during sedation, while reducing the total diazepam and post-operative analgesic dosages by 44% and 55%, respectively. Systolic, diastolic, and mean arterial blood pressures (MAP), as well as pulse rates, were reduced. Respiratory rate, oxygen saturation, end-tidal carbon dioxide, and recovery from sedation were unaffected. Patients, surgeons, and those administering the sedation preferred clonidine over the placebo. It was concluded that clonidine pre-treatment prolonged sedation and amnesia, and stabilized vital signs while significantly decreasing diazepam and post-operative analgesic usage.

In two recent 2012 studies (17, 18) authors compared the clinical effects of oral midazolam and oral clonidine. In the first study by Studer and colleagues (17), the researchers compared the anxiolytic and side effects of clonidine 150mcg (0.150 mg) and midazolam 7.5 mg for premedication in surgical wisdom tooth extraction in 10 adults. This study was a prospective, randomized, double-blind cross-over trial with the patients undergoing bilateral wisdom tooth extractions. Patients received clonidine 0.150mg or midazolam 7.5mg orally one hour before their treatment. Patients who received clonidine (C) for the first surgery received midazolam (M) at the second surgery and vice versa. The anxiolytic efficacy was evaluated with a visual analog scale (VAS) upon admission as well as 30, 50, and 60 minutes after administration of the medication. No other sedation (intravenous or nitrous oxide) was given following the oral doses of clonidine or midazolam. Following the administration of midazolam ($p<0.03$) or clonidine ($p<0.02$) after 30 minutes, an anxiolytic effect was recorded. No

statistically significant differences in anxiolytic effect (anxiety levels were reduced to the same) between the clonidine and midazolam groups were seen. No significant effects were seen on blood pressure and pulse. Similar side effects were reported, including: dizziness (3 in M group and 2 in C group), nausea (1 in M group and 1 in C group), slowing of mental performance and concentration (2 in M group), falling asleep (1 in C group), and mild collapse 20 minutes after discharge, which disappeared after being placed in a supine position for 2-3 minutes (1 in C group).

The second study (18) compared the clinical effects of oral midazolam and oral clonidine prior to general anesthesia in sixty ASA 1-2 children ranging in age from 2-8 years. Patients were randomly assigned to receive either oral clonidine (Group 1, n = 30, 4 mcg/kg) or oral midazolam (Group 2, n = 30, 0.5mg/kg) 60 minutes prior to the anesthesia induction. The two groups were similar with respect to age, weight, gender, ASA status, and duration of the surgery. The children judged the taste of clonidine as significantly better that the taste of midazolam ($p<0.05$). The onset of sedation was 38.5 minutes +/- 12 minutes in the clonidine group and 30.5 minutes +/-10 minutes in the midazolam group. However, the level of sedation and quality of the pre-operative anxiolysis was significantly better in the clonidine group compared to the midazolam group ($p<0.05$). The quality of parental separation (3 point scale where 1=poor [anxious or combative], 2=good [anxious but easily assured], and 3=excellent [calm/sleeping]) was significantly better in the clonidine group ($p<0.05$), as was mask acceptance for the general anesthesia ($p<0.05$). However, a satisfactory quality of induction was achieved in both groups. No adverse effects such as bradycardia, hypotension, hypoxemia, or apnea were observed during any of the pre-operative or the post-operative periods in either of the groups. Shivering was not seen in any of the patients in the clonidine group but was noted in the midazolam group (13.3%, significant).

The mechanism of clonidine in preventing shivering is correlated with the inhibition of vasoconstriction and a decrease in the shivering threshold (19). Post-operative nausea and

vomiting (PONV) were seen in 6.67% of patients in the clonidine group and in 10% of the patients in the midazolam group, though values were not significant.

As we can see in the results and conclusions of the studies, clonidine can be alternative of sedation and also can be pre-sedative agent but we need additional research to support these studies. In this study, we use clonidine at several doses as a pre-sedative and seek to determine if the clonidine regime can reduce the amount of sedation needed.

Methods

This study was a clinical, cross sectional study of patients in a major inner city dental clinic that provides free dental care to patients in financial need. Data were collected from treatment records completed from March 2012-April 2012. Many of the patients had a high level of dental anxiety and fear which made them ideal candidates for having dental care under moderate sedation. The study was voluntary since the patients could choose to participate or not after reading all possible side effects of clonidine and the consent form. The sedations and treatment of these patients were provided as part of an annual course offered to credential practicing dentists across the state and region to provide intravenous sedation in their dental practices.

All vital signs were taken in the waiting room as a part of the check-in process. There were 104 participants in the study. Of the 104 patients who were seen in the time period, 23 (14 female, 9 male) consented and met the inclusion criteria for clonidine treatment. Exclusion criteria included hypotension (blood pressure less than 100/70) and/or bradycardia (heart rate less than 60 beats per minute). Patients were also excluded if they had any of listed clonidine use precautions: kidney disease, heart disease (e.g. coronary artery disease, irregular heart rhythm, recent heart attack, depression, blood circulation disorders (e.g. Reynaud's disease, stroke), pregnancy or the consumption of alcoholic beverages. The remaining 81 patients did not receive clonidine treatment and were used as controls; one of them was excluded due to

inability to obtain intravenous access, therefore, there were only 80 controls and 103 total participants.

Gender, age, and body mass index were abstracted from the medical records. Patients were classified by the American Society of Anesthesiologists (ASA) physical status classification. This classification system is a system for determining the health condition of patients before surgery (20). The primary determining factor for ASA II status was smokers who smoked at least half a pack of cigarettes per day (ppd) for 1-30 years. Other medical conditions contributing to ASA status included hypertension, asthma, diabetes mellitus (type II), as well as a history of depression, drug and/or alcohol abuse, heart disease, and pulmonary conditions (COPD, bronchitis/emphysema).

Statistical analysis

All statistical analyses were conducted Using SAS. Descriptive statistics, including Chi-square tests, were conducted to examine the association between study sample characteristics and use of clonidine. An analysis of variance was undertaken with the Duncan's, Multiple Range Test for comparison of the hemodynamic changes (e.g. systolic, diastolic, mean arterial pressure, and pulse) of patients taking clonidine 0.1 mg, clonidine 0.2mg, and the control group. This comparison was done at four different times when the patients were seen and evaluated: 1) at the patients pre-assessment visit, typically one week prior to the sedation and dental procedures; and 2) 30 minutes to 1 hour following clonidine administration for the clonidine group, when the patient was brought to dental operative room for pre-sedation assessment, 3) intra-operatively: at the beginning of the parental sedation and dental procedure, and 4) intra-operatively: when the dental operative is almost done. During the intraoperative treatment, the patient's vital signs, oxygen saturation and level of consciousness were recorded every 5 minutes. Intraoperative sedation and treatment ranged from one to two and a half hours depending on the type of dental treatment provided. Treatment included extensive oral surgery, endodontic, operative, and periodontal treatment.

A comparison was done to determine if there is a significant difference between the two doses of clonidine regarding reduction in the amount of sedation. These doses were compared to those of the control group to find out the effectiveness of clonidine on sedation amount. These comparisons were evaluated by the Duncan's Multiple Range Test to determine if there are significant differences between means. Using the outcomes of these analysis, a simple regression model was generated. The model was refined using backward elimination to establish which variables should be kept and included in simple regression model. Based on these results, gender, ASA, and Fentanyl doses were eliminated. Age, body mass index, and Versed doses were retained in the model.

Results

Clinical observation

The first four patients who were given clonidine 0.2mg had significant hemodynamic changes prior to venipuncture. From the time they received clonidine 0.2 mg significant differences in BP, MAP and pulse changes occurred. In addition, in two of the four patients who received oral clonidine 0.2mg were reversed with Flumazenil (Romazicon) 0.2mg due to over sedation (as diagnosed by the administering dentist) at the end of their dental procedure. One patient had received 5mg IV midazolam, and the other 4mg IV midazolam and 25mcg of IV fentanyl. After this first day's experience, even though no other side effects were noted, such as PONV, fainting, light headiness, drowsiness, dry mouth, or complaints from the patients, it was decided to reduce the dose by half for the remainder of the patients electing to receive this pre-operation Sedatives.

Primary Results.

Of the 101 participants in the study, 49.5% female and 50.5% male. The number of participants in clonidine group was 23, with four of them having a dose of 0.2 mg and the remaining 19 receiving a dose of 0.1 mg. The control group, composed of 80 persons, had

slightly more males than females (53% males). The majority of the patients in the study (42% of total) were ages 44-56 years of age. Body mass index was categorized at five levels with underweight (16-18.5), normal (18.5-25), over weight (25.30), obese (30-35), and morbidly obese (35-40). More than half (54%) were overweight, obese, or morbidly obese.

The comparison of blood pressure (systolic and diastolic), pulse and mean arterial pressure (MAP) by levels of clonidine dose (0.2 mg and 0.1 mg and control) are given in Table 2. According to Duncan's Multiple Range Test, initially there is significant difference between mean systolic pressures for the clonidine 0.2 mg and 0.1m doses in comparison to the control group. At pre-sedation time, the clonidine 0.2 mg group had lower systolic and diastolic blood pressures than the 0.1 mg group and the control group. During first intraoperative period the results show systolic mean of 0.2 group was significantly lower than the control group. Finally, at the final intraoperative measurement, systolic and diastolic blood pressures were lower in the 0.2 mg group compared to the 0.1 mg group with the systolic blood pressure also lower than in the control group. With regard to pulse, 0.2mg group had a significantly higher initial pulse than the control group but not than the 0.1 mg group. The mean arterial pressure was significantly lower in the 0.2 mg group at pre-sedation and at the first intra-operative measurement in comparison to the 0.1 mg group and the controls.

The distribution of sedation agents by dose is given in Table 3 for the two levels of clonidine and the control group. Two drugs were the main intra-operative sedation and analgesic agents used: midazolam (Versed) (benzodiazepine) and Fentanyl (narcotic). Diphenhydramine (Benadryl) was added in some cases for the patients when more sedation was felt necessary and the maximum number of other agents had been reached. The maximum dose of drugs given to the dentists to use per patient (due to the course format and pharmacy constraints) was midazolam 10mg and fentanyl 100mcg. However, the cases had treatment planned and if the case extended over 90 minutes, more sedative/analgesic agents could be requested and used. The result shows no significant difference in the use of sedation drugs by the three drug exposure groups, although the data did suggest more sedatives were required at lower clonidine doses.

Finally, Table 4 shows the adjusted model, we can see that after adjusted for age, BMI, and dose of Versed administered, mean systolic blood pressures for the 0.2 mg clonidine dose group are significantly lower at pre- sedation and the first intraoperative times in comparison to the 0.1 mg group and the controls. Diastolic blood pressures were not different by the three groups after adjustment in the model.

Discussion

The purpose of this study was to investigate clonidine as a pre-operative sedative agent prior to moderate sedation in dentistry, by considering its advantages as an alpha -2 adrenergic agonists. The data were analyzed to compare means of vital signs and amount of sedation needed for clonidine (0.2mg, 0.1mg) and control groups. This comparison was done to find out if clonidine can lower vital signs at a safe level and reduce the amount of sedation needed as well. As noted in the previous discussion (literature review), the literature varied on the recommended dosing for adults (See appendix table).

Although reductions in BP, MAP and pulse did occur with the pre-sedation clonidine 0.2mg dose, the differences were not as significant in the 19 patients who took the clonidine 0.1mg when compared to control. However, given the very small numbers of subjects in the 0.2 mg clonidine group (N=4), the power is very limited. The only statistically significant effect from the adjusted means in the model was the marked reduction in systolic blood pressure in the clonidine 0.2 mg group. In comparison to the control group, which as the most stable mean blood pressure values (N=80), the reduction is a 23 mm Hg for systolic pressure at pre-sedation and a 23mg Hg decrease at the first intraoperative measurement. Although there was some indication that smaller doses of sedatives (Versed and Fentanyl) were used for the clonidine groups, the study was not large enough to demonstrate statistically significant differences.

Comparison to previous studies.

The majority of previous studies were examining the use of clonidine as a pre-sedative in dentistry were conducted using a randomized, double-blind design. In most of these studies, clonidine was found to be an effective pre-sedative with few side effects. Systolic, diastolic, and mean arterial blood pressures (MAP), as well as pulse rates, were reduced with the use of clonidine in these studies. It is challenging to compare the results of this study since the design did not randomize patients to different medication groups and only 23 of the patients received clonidine (and only 4 at the highest dose groups). The change in the administered dose followed the reporting of changes in blood pressure, Map, and pulse rate in the initial four patients, so the dose was lowered to 0.1 mg in the remaining patients. In general, previous studies did not show side effects at this dose level. These limitations challenge the comparison with previous studies.

Strengths and Limitations.

This study has many limitations. One main limitation was lack of statistical power due to small sample size of all clonidine groups but specifically for the 0.2 dose group. Originally the purpose of the study was to examine the effect of 0.2 mg dose on blood pressure and required sedation, but as mentioned some minor side effects were occurring in patients which led to a reduction in the dose for the remaining patients. Additional covariates like race and health status were not collected in the study nor controlled in the analysis. Therefore, the study population is not representative of overall population. Participation was based on convenience sampling and therefore random selection and blinding were not employed in the design of the study.

Conclusions and directions for future research.

This study did not find that the use of clonidine led to a significant reduction in the amount of sedation medication needed. The mean systolic blood pressures for the 0.2 mg clonidine dose group were significantly lower at pre- sedation and the first intraoperative times in comparison to the 0.1 mg group and the controls in the adjusted model; however, there were no significant differences across the measurement times for the effect of clonidine on diastolic blood pressure.

This study suggests that there are complications in using clonidine at the 0.2 mg dose level. Reduction to the 0.1 dose level lessened the complications but may have reduced the effectiveness of the drug as a pre-sedative.

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Appendix Table

Recommended Adult Dosing for Clonidine (literature review)

Recommended Pre-med Clonidine dose	Milligram (mg) for 70 kg person	Reference Number from bibliography	Author and Journal
0.2 mg 0.1 mg (elderly)	0.2 mg	1.	David Todd. ADSA. The pulse.
0.2 mg	0.2 mg	3.	Hall et al. Anesthesia Progress. (2006) 53:34-42.
5mcg/kg	0.35 mg	5.	Murai et al. Anesthesia Progress. (1995) 42:135-138.
150 mcg	0.15 mg	6.	Fanini et al. Mineral Stomatol. (1998) 47(9):459-64.
5mcg/kg	0.35 mg	7.	Frank et al. Anasthesiol Intensivmed Notfallmed Schmerzther. (2000) 35(7):428-34.
1.5 mcg/kg 2.0 mcg/kg	0.105 mg 0.14 mg	8.	Mutzbauer et al. Schweiz Monatsschr Zahnmed (2005) 115(3):214-218. (in German)
0.1 mg/35 kg	0.2 mg	9.	Hall et al. Journal of Dental Research (2006) 85 (9): 854-858.
150 mcg	0.15 mg	10.	Studer et al. Oral Maxillofac Surg (2012) 16: 341-347.
4.0 mcg/kg* Avg. wt. 2yrs =28.4 lbs; or 12.9 kg Avg. wt. 8 yrs = 57.2 lbs; or 25.9 kg	Ranges= 0.1 mg 0.2 mg	11.	Mahajan et al. J. of Clinical and Diagnostic Research (2012) 6(5): 870-873.

Acknowledgements

First and foremost, I would like to thank my chair and mentor, Dr. Wayne Sanderson for guidance throughout the capstone process and especially for extensive help in the analysis of the data. Without his support, I would certainly not have finished this project.

I would like to thank Dr. Henry, from the College of Dentistry, who provide me with the data for this project and Drs. Lorie Chesnut and Mel Kantor who assisted me early on in the process. I would also like to thank Dr. Steve Browning and Dr. Steve Fleming for reviewing my capstone, offering comments and suggestions, and serving on my committee.

Dr. Corinne Williams, Director of the MPH program, handled the administrative details for my degree program and encouraged me to complete the degree.

I have no financial or material supports to disclose for this project.

Biographical Sketch

Asma Kamur received her Bachelor degree from _Tripoli university, college of Dentistry. _____

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Table 1: Study Population Demographics					
Characteristics	**Overall N=102 N (%)**	**Clonidine 0.1 mg N=19 N (%)**	**Clonidine 0.2 mg N=4 N (%)**	**Control N=80 N (%)**	**P-value#**
Sex					
Female	50 (49.5)	10 (20)	4 (8)	36 (72)	0.05
Male	51 (50.5)	9 (17.7)	0 (0)	42 (82.3)	
Age					
18-30	19 (18.81)	1 (5.2)	1 (5.3)	17 (89.4)	0.49
31-43	29 (22.7)	6 (21.4)	2 (7.1)	20 (71.4)	
44-56	42(41.5)	9(21.4)	1 (2.4)	32 (76)	
>=57	12 (11.9)	3 (25)	0 (0)	9 (75)	
BMI *					
16-18.5	8 (7.8)	0(0)	0 (0)	8 (100)	0.033
18.5-25	39 (37.8)	10 (25.6)	3 (7.7)	26 (66.7)	
25-30	24 (23.3)	2 (8.33)	0 (0)	22 (91.7)	
30-35	27 (26.2)	5 (18.52)	0 (0)	22 (81.5)	
35-40	5 (4.8)	2 (40)	1 (20)	2 (40)	
ASA Status ~					
I	16 (15.5)	1 (6.25)	0 (0)	15 (93.7)	0.27
II	74 (71.8)	17 (23)	4 (5.4)	53 (71.6)	
III	12 (11.6)	1 (8.3)	0 (0)	11 (91.7)	
IV	1 (0.8)	0 (0)	0 (0)	1 (100)	

*Body mass index
~ American Society of Anesthesiologist physical status classification
# P value refer to Likelihood Ratio Chi-Square test.
Effective sample size =101; Frequency missing =2

Table 2: Comparison of Hemodynamic Changes among the Participants (N=103)			
BLOOD PRESSURE PULSE MAP*	**Clonidine 0.1 mg N=19**	**Clonidine 0.2 mg N=4**	**Control N=80**
INITIAL	152^{A} / 89^{A} 81^{AB}	121^{B} / 83^{A} 92^{A}	135^{AB} / 80^{A} 77^{B}
PRE-SEDATION	133^{A} / 80^{A} 75^{A} 97^{A}	97^{B} / 66^{B} 85^{A} 77^{B}	126^{A} / 77^{A} 78^{A} 93^{A}
FIRST INTRA - OPERATIVE	117^{AB} / 73^{A} 78^{A} 98^{A}	102^{B} / 69^{A} 77^{A} 77^{B}	121^{A} / 73^{A} 78^{A} 94^{A}
FINAL INTRA-OPERATIVE	131^{A} / 81^{A} 74^{A} 89^{A}	96^{B} / 67^{B} 80^{A} 80^{A}	126^{A} / 77^{AB} 78^{A} 89^{A}

* MAP=Mean arterial blood pressure

The symbols letters $^{A, B, \text{and } AB}$ indicate significant differences in means according to Duncan's Multiple Range Test; means with the same letters are not significantly different from each other.

Table3: Sedation Administration Among the Participants N=103				
Sedative Agent	**Clonidine 0.1 mg Mean effective [A] N=19 N (%)**	**Clonidine 0.2 mg Mean effective [A] N=4 N (%)**	**Control Mean effective[A] N=80 N (%)**	**P value**
VERSED				0.502
	6[A]	4[A]	6[A]	
<=5	9(47)	3(75)	39(48)	
5-10	9(47)	1(25)	37(46)	
>10	1(5.3)	0(0)	2(2.5)	
FENTANYL				0.41
	63[A]	25[A]	71[A]	
2-50	6(31)	2(50)	10(12.5)	
75-175	8(42)	1(25)	31(38.8)	

Table4: Adjusted Means - Systolic and Diastolic Blood Pressure Measurements by Clonidine Levels				
	Clonidine 0.1 mg N=19	**Clonidine 0.2 mg N=4**	**Control N=80**	**P value**
Pre-Sedation				
Systolic Pressure	131^{A}	104^{B}	127^{A}	0.017
Diastolic Pressure	79	70	78	0.290
Intra-Operative (First)				
Systolic Pressure	128^{A}	103^{B}	126^{A}	0.041
Diastolic Pressure	80	71	77	0.411
Intra-operative (Final)				
Systolic Pressure	115	107	121	0.142
Diastolic Pressure	72	72	73	0.862

Means adjusted for age, body mass index, and the dose of versed administered.

The symbols letters $^{A.B.\ AB}$ According to Duncan, s Multiple Rang Test, means with the same letters are not significantly different from each other.