*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*
*e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 8 Ser. 6 (August. 2019), PP 36-41*
*www.iosrjournals.org*

# Comparison of Glycaemic Control with Oral Diazepam and Oral Clonidine as Premedicants in Elective Orthopaedic Procedures

DrKolati V L Suneetha[1]Dr T Suhasini[2]Dr T Radha Rani[3]
*Assistant Professor, Department of Anaesthesiology, Rangaraya Medical College, Kakinada, Andhra Pradesh, India*
*Former Additional Professor, Department of Anaesthesiology, Nizam's Institute of Medical Sciences,Hyderabad,India*
*Former Assistant Professor, Department of Anaesthesiology, Nizam's Institute of Medical Sciences, Hyderabad, India*
*Corresponding Author: Dr Kolati V L Suneetha*

***Abstract**: Stress response to anaesthesia and surgery is a well-known entity involving hormonal and metabolic disturbances. Pre-operative medication is an important part of anaesthesia. Satisfactory preoperative preparation and medication facilitates an uneventful perioperative course.Administration of $\alpha_2$-adrenoceptor agonists generally increase blood glucose levels, in spite of the ensuing sympatholysis that would be expected to lower blood glucose as a result of diminished $\alpha_1$- and $\beta$-adrenoceptor activation. This class of drugs has been investigated in almost all facets of anaesthesia practice like premedication, intraoperative supplementation, total intravenous anaesthesia, intraoperative haemodynamic control and induced hypotension, postoperative analgesia, as an adjunct or alone for regional anaesthesia and analgesia. Clonidine has two opposing effects on blood glucose[10]. On the one hand it suppresses the stress responses to surgery by decreasing sympathoadrenal outflow. This property of clonidine may attenuate the increase in plasma glucose in response to surgery. But clonidine also inhibits the release of insulin and potentiates the secretion of growth hormone. The modification of these two hormones by clonidinemay contribute to the increase in plasma glucose concentrations.To test this hypothesis, this study was undertaken to compare the effect of oral clonidine and oral diazepam on blood glucose levels.*

*This prospective, controlled, randomized, double blind study was conducted in 53 ASA PS I and II patients undergoing elective orthopaedic procedures under general anaesthesiato evaluate the glycaemic control with either diazepam(group 1) or clonidine (group 2) premedication.In our study, we observed that there was no statistically significant difference in the glycaemic control.*

---

Date of Submission: 29-07-2019 Date of Acceptance: 14-08-2019

---

## I. Introduction

Stress response to anaesthesia and surgery is a well-known entity involving hormonal and metabolic disturbances[1]. Pre-operative medication is an important part of anaesthesia. Satisfactory preoperative preparation and medication facilitates an uneventful perioperative course. An ideal premedicant should achieve the goals like reduction of fear and anxiety, potentiation of anaesthesia and amnesia; diminishing the dosages and side effects of anaesthetic agents; reducing the unwanted reflex activity during surgery and ensuring a smooth recovery.

Benzodiazepines, the routinely used premedication, are associated with unwanted side effects like central nervous depression, do not provide analgesia and have metabolites with long half-lives so that the adverse effects may persist well into the postoperative period. Alpha-2 agonists have attracted increasing interest as adjuncts to anaesthesia recently. A variety of beneficial effects before, during and after anaesthesia are noted. The $\alpha_{2A}$-adrenoceptor has been identified as an important regulator of blood glucose homeostasis. $\alpha_{2A}$-Adrenoceptors on pancreatic β-cells inhibit insulin secretion, and $\alpha_{2A}$-adrenoceptors on sympathetic nerves and on adrenomedullarychromaffin cells limit sympathoadrenal output. Recently, human $\alpha_{2A}$-adrenoceptor gene polymorphisms that influence $\alpha_{2A}$-adrenoceptor expression and function have been described. Increased $\alpha_{2A}$-adrenoceptor expression has been associated with impaired glucose-stimulated insulin secretion, elevated fasting blood glucose levels and an increased risk of type 2 diabetes. Accordingly, administration of $\alpha_2$-adrenoceptor agonists generally increases blood glucose levels, in spite of the ensuing sympatholysis that would be expected to lower blood glucose as a result of diminished $\alpha_1$- and β-adrenoceptor activation This class of drugs has been investigated in almost all facets of anaesthesia practice like premedication, intraoperative supplementation, total intravenous anaesthesia, intraoperative haemodynamic control and induced hypotension,

postoperative analgesia, as an adjunct or alone for regional anaesthesia and analgesia. The pharmacodynamic profile of these agents makes them the most ideal adjuvant for clinical anaesthesia.The drug has two opposing effects on blood glucose[10]. On the one hand it suppresses the stress responses to surgery by decreasing sympathoadrenal outflow. Premedication with clonidine inhibits the release of catecholamines and cortisol during surgery in adults and attenuates catecholamines response to tracheal intubation in children. This property of clonidine may attenuate the increase in plasma glucose in response to surgery. But clonidine also inhibits the release of insulin and potentiates the secretion of growth hormone. The modification of these two hormones by clonidine may contribute to the increase in plasma glucose concentrations.To test this hypothesis, this study was undertaken to compare the effect of oral clonidine and oral diazepam on blood glucose levels.

## II. Materials and methods

This prospective, randomized, controlled, double blind study has been undertaken after Institutional Ethical Committee approval. An informed consent was obtained from all the patients included in the study. Fifty-three patients of either gender, 18-45 years belonging to American Society of Anesthesiologists physical status I or II scheduled for electiveorthopaedic surgery requiring general anaesthesia expected to last less than 3 hours were randomly divided into two groups, diazepam (group 1) and clonidine (group 2). Allocation of patients to each group was made according to the random numbers generated by Minitab Statistical Software. The exclusion criteria were patients with cardiovascular diseases like hypertension,diabetes mellitus,valvular heart disease, coronary heart disease, history of convulsions, neurological deficits, chronic obstructive pulmonary disease, anticipated airway problems, patients with risk of aspiration and pregnancy.

Following overnight fasting, patients were premedicated with either tablet clonidine 200 micrograms or diazepam 5 mg 2 hours prior to surgery. In the operating room, an intravenous cannula was placed under local anaesthesia and standard monitoring was established.

All patients were induced with a standard anaesthetic technique which included 2microgms/kg of Fentanyl and 5mg/kg of 2.5% Thiopentone sodium given intravenously. Endotracheal intubation was done after skeletal muscle paralysis with rocuronium in the dose of 0.9mg/kg body weight, intravenously. All patients were ventilated with 60% nitrous oxide and 40% oxygen with a tidal volume of 6-8 ml/kg and a rate of 12-14 breaths per minute. Skeletal muscle relaxation was maintained with rocuronium administered in bolus doses.Inhalational anaestheticsevoflurane was titrated as per haemodynamicresponse. Blood Glucose measurements taken at baseline(before administering premedication), induction and at one, three, five minutes , at incision, 30 minutes, 60 minutes, 90 minutes and 120 minutes after endotracheal intubation and at extubation and 5minutes post-extubation. Extubation was done after reversal of residual neuromuscular blockade with Inj neostigmine 0.05mg/kg and Injglycopyrrolate 10microgms/kg. Postoperatively i.e immediately before shifting to recovery room, all patients received injparacetamol 1g intravenously.

The parameters compared wereblood glucose measurements taken at baseline(before administering premedication) induction and at one, three, five minutes, at incision, 30 minutes, 60 minutes, 90 minutes and 120 minutes after endotracheal intubation and at extubation and 5minutes post-extubation.

Statistical analysis was done for the data upto 30 minutes post-intubation. Categorical data, ordinal data and continuous data were analyzed using Chi-square test, Mann-Whitney U test, and parametric tests respectively. The distinct use of non-parametric vs parametric tests was made after evaluating the data with boxplots and distribution of data. Among the parametric tests, data between the two groups were analyzed by Student's t-test.

## III. Results

A total number of fifty-three patients were randomly assigned into clonidine and diazepam groups. The demographic data between the two groups: group 1 (diazepam) and group 2 (clonidine) as shown in Table 1 (age, gender, weight, duration of and surgery) were comparable between the two groups.

Demographic data: **Table 1**

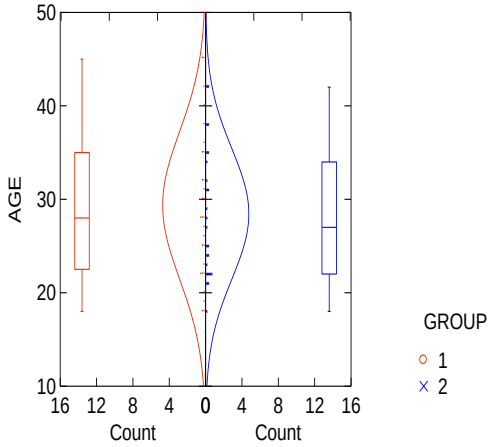
| Demographic data | Group | Age(years) | Weight(kg) | Duration of surgery(min) |
|---|---|---|---|---|
| Diazepam | Mean<br>SD<br>Diff in means and 95% CI<br>p-value | 29.35<br>7.88<br>0.92(-3.18 to 5.02)<br>0.656 | 58.42<br>9.08<br>0.27(-4.68 to 5.22)<br>0.914 | 91.96<br>33.50<br>9.96(- 8.07 to 27.99)<br>0.273 |
| Clonidine | Mean<br>SD<br>Diff in means and 95% CI<br>p-value | 28.44<br>6.99<br>0.92(-3.18 to 5.02)<br>0.656 | 58.16<br>8.86<br>0.27(-4.68 to 5.22)<br>0.914 | 82.00<br>31.85<br>9.96(- 8.07 to 27.99)<br>0.273 |

Comparison of age between the two groups group1 (diazepam) and group 2(clonidine) as shown in Table-1, Fig-1.

**Table-1**

| **Age distribution** | | | | | |
|---|---|---|---|---|---|
| ***Group*** | ***N*** | ***Mean*** | ***SD*** | ***CI*** | ***p-value*** |
| Diazepam | 28 | 29.35 | 7.88 | -3.18 to 5.02 | 0.656 |
| Clonidine | 25 | 28.44 | 6.99 | -3.21 to 5.04 | 0.658 |

**Fig-1**

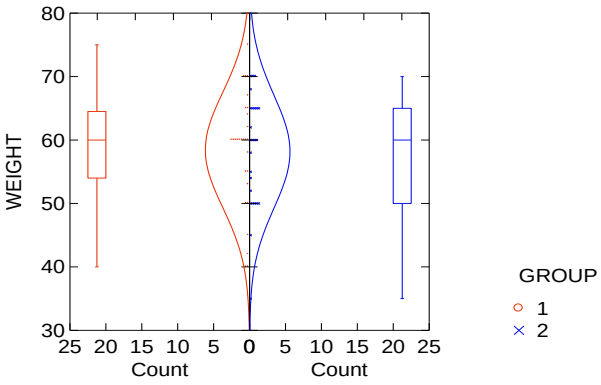



Comparison of weightbetween the two groups, group-1 and group-2 as shown in Table-2, There is no statistically significant difference.

**Table-2**

| **Weight distribution** | | | | | |
|---|---|---|---|---|---|
| ***Group*** | ***N*** | ***Mean*** | ***SD*** | ***CI*** | ***p-value*** |
| Diazepam | 28 | 58.42 | 9.08 | -4.68 to 5.22 | 0.914 |
| Clonidine | 25 | 58.16 | 8.86 | -4.69 to 5.23 | 0.914 |

**Fig-2**

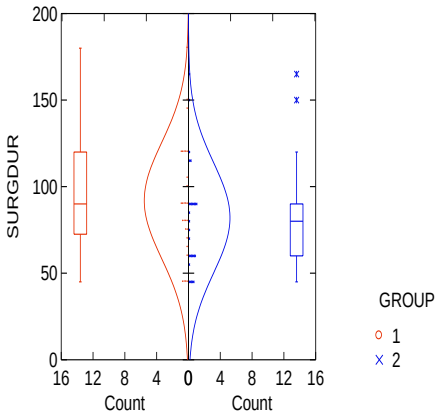



Comparison of duration of surgerybetween the two groups as shown in Table-3, Fig-3. There is no statistically significant difference.

**Table-3**

| ***Duration of Surgery*** | | | | | |
|---|---|---|---|---|---|
| ***Group*** | ***N*** | ***Mean*** | ***SD*** | ***CI*** | ***p-value*** |
| Diazepam | 28 | 91.96 | 33.50 | - 8.07 to 27.99 | 0.273 |
| Clonidine | 25 | 82.00 | 31.85 | - 8.12 to 28.05 | 0.274 |

**Fig-3**




The anaesthetic technique was standardized. Glycaemic control- the blood glucose estimations done during the preoperative, preinduction, at intubation and during surgery were similar in both the groups as shown in Table The blood sugar levels during the immediate post extubation period were significantly less in clonidine group.

**Table 4**

| Time period | Diazepam (Mean ± SD) | Clonidine (Mean ± SD) | Diff in means (95% CI) | P value |
|---|---|---|---|---|
| **Baseline** | 103.18(19.32) | 108.88(14.41) | -5.70(-15.05 to3.65) | 0.226(NS) |
| **At intubation** | 98.86(23.05) | 99.20(14.59) | -0.34(-10.89 to10.21) | 0.948(NS) |
| **Post intubation 1min** | 113.00(14.95) | 107.36(16.55) | 5.64(-3.11 to14.39) | 0.201(NS) |
| **Post intubation 3min** | 105.39(17.56) | 97.40(14.31) | 7.99(-0.81 to16.79) | 0.074(NS) |
| **Post intubation 5min** | 98.04(20.69) | 97.68(16.85) | 0.36(-10.01 to10.72) | 0.945(NS) |
| **At incision** | 104.54(21.02) | 99.72(13.27) | 4.82(-4.80to14.43) | 0.319(NS) |
| **Post intubation 30 min** | 104.14(23.65) | 106.00(14.93) | -1.86(-12.68 to8.96) | 0.731(NS) |
| **At extubation** | 121.04(20.17) | 104.72(10.15) | 16.32(7.59 to25.04) | 0.001 |
| **Post ext 5min** | 126.32(25.44) | 115.00(20.90) | 11.32(-1.47to24.11) | 0.082(NS) |

**Fig 4**

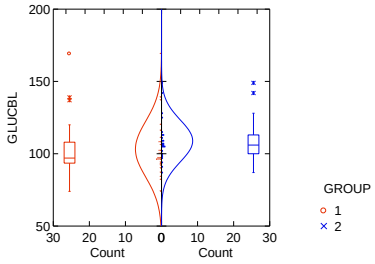



**Fig 5**

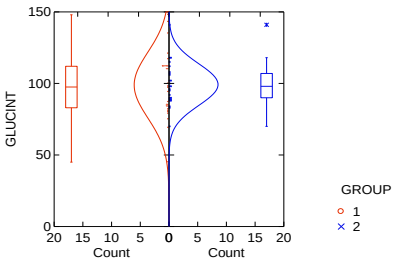



**Fig 6**

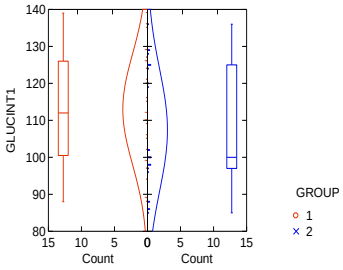



**Fig 7**

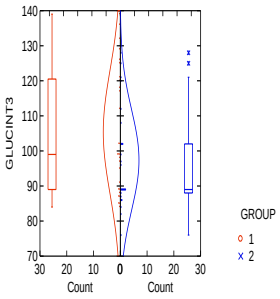



**Fig 8**

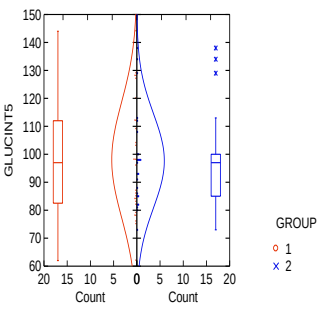



**Fig 9**

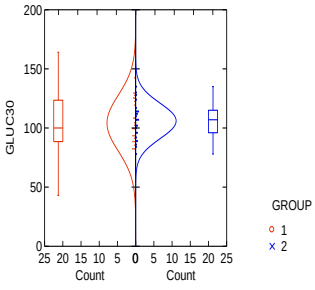
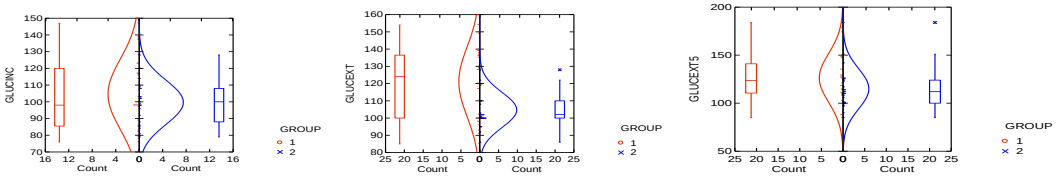
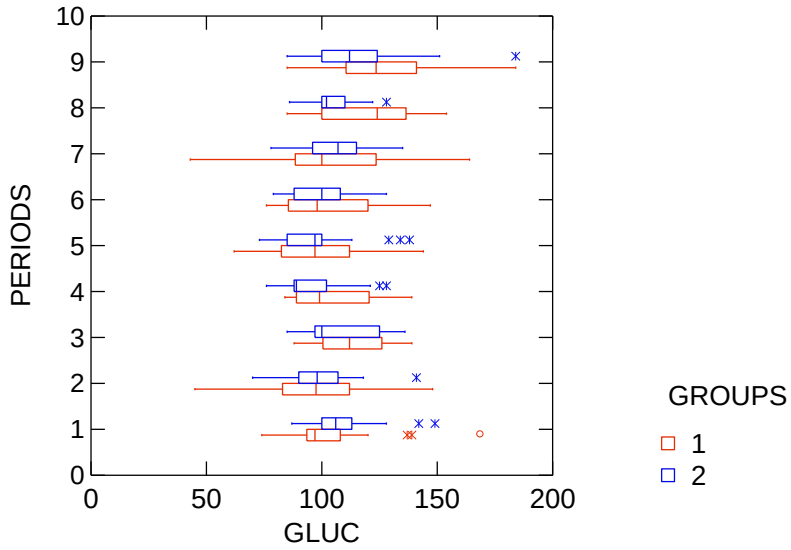


**Fig 10** **Fig 11** **Fig 12**




Comparison of Blood glucose changes during various periods between the two groups as depicted by the overlay box

**Fig 13**




## IV. Discussion

This study was undertaken to evaluate the efficacy of oral Clonidine and oral diazepam in controlling blood glucose levels. The $\alpha_{2A}$-adrenoceptor has been identified as an important regulator of blood glucose homeostasis[2]. $\alpha_{2A}$-Adrenoceptors on pancreatic β-cells inhibit insulin secretion, and $\alpha_{2A}$-adrenoceptors on sympathetic nerves and on adrenomedullarychromaffin cells limit sympathoadrenal output. Recently, human $\alpha_{2A}$-adrenoceptor gene polymorphisms that influence $\alpha_{2A}$-adrenoceptor expression and function have been described. Increased $\alpha_{2A}$-adrenoceptor expression has been associated with impaired glucose-stimulated insulin secretion, elevated fasting blood glucose levels and an increased risk of type 2 diabetes[8]. Accordingly, administration of $\alpha_2$-adrenoceptor agonists generally increases blood glucose levels, in spite of the ensuing sympatholysis that would be expected to lower blood glucose as a result of diminished $\alpha_1$- and β-adrenoceptor activation.

Amongst the many agents, benzodiazepines (especially diazepam) and atropine have been used for a long time. Recently clonidine, a centrally acting alpha-2 agonist, has attracted increasing interest as an adjuvant to anaesthesia. A variety of beneficial effects before, during and after anaesthesia, such as sedation, anxiolysis and antisialagogue action, analgesia, increased cardiovascular stability and improved outcome, have been attributed to clonidine[2,3,4] . This class of drugs has been investigated in almost all facets of anaesthesia practice like premedication, intraoperative supplementation, Total Intravenous Anaesthesia (TIVA), intraoperative haemodynamic control and induced hypotension, postoperative analgesia, as an adjunct or alone for regionalanaesthesia and analgesia.

Clonidine is available as 0.1mg tablets. Intravenous preparation is not available freely in our country. The sedation with clonidine is dose related. It has been reported by Carabine P. Wright et al that premedication with 0.3mg of clonidine is associated with high degree of sedation when compared to 0.1 and 0.2mg and also caused significant bradycardia and hypotension[6]. Hence we have used 0.2mg as premedicant dose. The varying difference in the haemodynamic response to different doses of clonidine could be due to the therapeutic window as very large and smaller doses produce less effect on arterial pressure.

It has been proven that the cardiovascular changes are caused by the combination of effects on central apha-2 and peripheral alpha-1 receptors. The alpha-2 adrenergic effects are more pronounced in smaller doses while with larger doses alpha-1 effects predominate.

Premedication with alpha-2 agonists, has several advantages over benzodiazepines. They have two opposing effects on blood glucose.[10] On the one hand it suppresses the stress responses to surgery by decreasing sympathoadrenal outflow. Premedication with clonidine inhibits the release of catecholamines and cortisol during surgery in adults and attenuates catecholamines response to tracheal intubation in children. This property of clonidine may attenuate the increase in plasma glucose in response to surgery. But clonidine also inhibits the release of insulin and potentiates the secretion of growth hormone. The modification of these two hormones by clonidine may contribute to the increase in plasma glucose concentrations.To study this hypothesis,Nishina, K et al have investigated the effect of oral clonidine on plasma glucose homeostasis[10]and found that oral clonidine premedication attenuated the hyperglycemic response to surgery and glucose infusion.

Flacke et al have observed improved haemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. They found reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery,also evidenced myocardial ischaemia as observed by ST-T changes developed in patients who did not receive clonidine[5]. We foundglycaemic control was comparable.

Lattermann et al have found thatPremedication with clonidine 1 $\mu g \cdot kg^{-1}$ accentuates the hyperglycemic response to lower abdominal surgery caused by the decrease in insulin plasma concentrations[9].

Devedjian, JC, et al.studied and found that overexpression of alpha2-adrenoceptors in beta cells can lead to impaired insulin secretion and glucose intolerance inTransgenic mice[7].

Rosengren, AH, et al. studied and found that overexpression of alpha2A-adrenergic receptors contributes to type 2 diabetes[8].

Gaumann et al studied cardiovascular and endocrine effects of clonidine premedicationVs placebo in neurosurgical patients and found plasma catecholamine concentrations did not differ between the two groups. Plasma glucose concentrations increased in both groups at the end of the study (P less than 0.05), but were lower in clonidine-treated patients (P less than 0.05)[11]

In Contrary to above studies, we found no difference in glycaemic control in Diazepam Vs Clonidine premedicated patients.

## V. Conclusion

In this study, we have evaluated the glycaemic control of oral clonidine and diazepam given as premedication in elective orthopaedic procedures under general anaesthesia. Patients in both the groups maintained blood glucose within preoperative range.We found that there was no statistically significant difference between the two groups.

## References


[1]. J.P.Desborough. The stress response to trauma and surgery. Br J Anaesth 2000; 85: 109–17.
[2]. Maze M, Tranquilli W: Alpha-2 adrenoceptor agonists: Defining the role in clinical anesthesia. Anesthesiology 1991; 74: 581–605.
[3]. TakahiKoKamibayashi and Maze M et al. The role of Alpha2-adrenergic agonists in Anesthesia. Recent Advances in Anaesthesia and Analgesia No 21; 1-15.
[4]. Hayashi Y, and Maze M: Alpha-2 adrenoceptor agonists and anaesthesia. Br JAnaesth 1993; 71: 108–118.
[5]. Flacke JW, Bloor BC, Flacke WE, Wong D, Dazza S, Stead SW, Laks H. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 1987; 67:11-19.
[6]. U.A. Carabine, P.M.C.Wright and J. Moore. Pre-anaesthetic medication with clonidine: A dose response study. British Journal of Anaesthesia1991; 67:79-83.
[7]. Devedjian, JC, Pujol, A, Cayla, C, George, M, Casellas, A, Paris, H *et al.* Transgenic mice overexpressing alpha2A-adrenoceptors in pancreatic beta-cells show altered regulation of glucose homeostasis. Diabetologia 2000; 43: 899– 906.
[8]. Rosengren, AH, Jokubka, R, Tojjar, D, Granhall, C, Hansson, O, Li, DQ *et al.* Overexpression of alpha2A-adrenergic receptors contributes to type 2 diabetes. *Science* 2010; **327**: 217– 20
[9]. Lattermann, R, Schricker, T, Georgieff, M, Schreiber, M. Low dose clonidine premedication accentuates the hyperglycemic response to surgery. *Can J Anaesth* 2001; 48: *755*– 9.
[10]. Nishina, K, Mikawa, K, Maekawa, N, Shiga, M, Obara, H. Effects of oral clonidine premedication on plasma glucose and lipid homeostasis associated with exogenous glucose infusion in children.*Anesthesiology* 1998; 88: 922– 7.
[11]. Gaumann DM, Tassonyi E, Rivest RW, Fathi M, Reverdin AF: Cardiovascular and endocrine effects of clonidine premedication in neurosurgical patients. Can J Anaesth 1991; 38:837-43.


Dr Kolati V L Suneetha. "Comparison of Glycaemic Control with Oral Diazepam and Oral Clonidine as Premedicants in Elective Orthopaedic Procedures." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 8, 2019, pp 36-41.