European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 9, Issue 4, Summer 2022

ORIGINAL RESEARCH

To Compare The Perioperative Benefits Of Oral Midazolam And Oral Clonidine In Patients Undergoing Major Abdominal Surgeries Under General Anaesthesia

[1]Dipty Agrawal, [2]Jugal Kishor Agarwal, [3]Aijaz Ahmad, [4]Vinay Sharma

[1]Assistant Professor, Department of Anesthesia, Rama Medical College Hospital and Research Center, Pilkhuwa, Hapur, Uttar Pradesh, India
[2]Assistant Professor, Department of Microbiology, Rama Medical College Hospital and Research Center, Pilkhuwa, Hapur, Uttar Pradesh, India
[3]Assistant Professor cum Statistician, Department of Community Medicine, Rama Medical College Hospital and Research Center, Pilkhuwa, Hapur, Uttar Pradesh, India
[4]Professor & Head, Department of Pharmacology, Rama Medical College Hospital and Research Center, Pilkhuwa, Hapur, Uttar Pradesh, India

Correspondence:
Dipty Agrawal
Assistant Professor, Department of Anesthesia, Rama Medical College Hospital and Research Center, Pilkhuwa, Hapur, Uttar Pradesh, India
Email: drjugalkishore9@gmail.com

ABSTRACT

Background: One of the challenges for anaesthesiologists is to minimize distress for patients in the operating room (OR) environment and to facilitate a smooth induction of anesthesia.A sedative drug is given before transfer to the OR. The beneficial effects of anxiolytic are sedation, anxiolysis, reduction of postoperative vomiting andpostoperative emergence phenomenon. Clonidine, an α 2-agonist, have been suggested as another option for premedication as effective as midazolam.

Materials and Methods: 50 patients were randomly divided into two groups.To one group Tab. Midazolam 7.5 mg was given while to other group Tab. Clonidine 100 µg was given one hour before induction ofanesthesia.Patients were evaluated and compared for benefits of preoperative oral midazolam and oral clonidine on sedation scores, perioperative hemodynamic parameters and perioperative opioid and analgesic requirement. Independent sample t-test was used and p-value < 0.05 was considered significant.

Results: We found that mean OAA/S sedation score in clonidine group was 11.48 ± 1.12 than in midazolam group13.68 ±1.03withsignificant difference ofp value (p<0.001).There was significant (P < 0.05) attenuation of hemodynamic response to intubation, surgical stress response and extubation with clonidine as compared to midazolam .None of the patients desaturatedin either group. Opioid

requirement(72%)was more in midazolam group as compared to clonidine (28%)group. Recovery in clonidine group took slightly longer time 60.00 ± 13.77min as compared to midazolam group 44.40±13.25 min.

Conclusion: Premedication with 100 micrograms of oral clonidine can reasonably be recommended as premedication in ASA I and II patients for all surgeries to provide more sedation, stable hemodynamics intraoperatively, reduction in stress response,less opioid consumption.

Keywords: Clonidine, Midazolam, Opioid, Premedication, Anxiolytic. American Society of Anesthesia (ASA).

INTRODUCTION

Anxiolysis is main part of premedication in patients undergoing major surgeries which effects pre, intra and postoperative outcome of surgery.Thebenzodiazepine midazolam,an anxiolytic drug, is the most commonly used premedication [1,2]. Premedication with midazolam had shown to be effective in reducing anxiety and improving compliance at induction of anesthesia. The beneficial effects of midazolam include sedation, anxiolysis, and reduction of postoperative vomiting[3], fast onset and limited duration of action.A recent evidence-based clinical update had shown that oral midazolam 0.5 mg/kg is effective in reducing anxiety in children, with minimal effect on recovery time[4].However, it causes postoperative behavior changes, cognitive impairment [5], paradoxical reactions, and respiratory depression [6].Clonidine, an α 2-agonist, have been suggested as another option for premedication and previous studies have shown it to be equally as effective as midazolam. Oral clonidine premedication has also been shown to reduce the incidence of sevoflurane induced emergence agitation A variety of beneficial effects before, during and after anesthesia, such as sedation, analgesia, increased cardiovascular stability and improved outcome, have been attributed to clonidine. Clonidine reduced the requirement for volatile anesthetics when assessed by hemodynamic responses[7,8].

A national survey of premedication practices conducted by Kain et al[9]shows thatMidazolam is that it is most commonly ordered premedication in pediatric anesthesia. The benefits of effective premedication include a reduction in both patient and parental separation anxiety, partial anterograde amnesia, facilitation of a smooth anesthetic induction, and a reduction in postoperative behavioral change, however similar investigations in the adult population had not been conducted. We therefore evaluated and compared the effect of 7.5mg of oral midazolam and 100 µg of oral clonidine premedication in healthy adult surgical patients by using the Observer's Assessment of Alertness/Sedation Scale (OAA/S) preoperatively and the hemodynamic response and intra operative and post operative analgesic requirement.

MATERIALS AND METHODS

This study was conducted in the Department of Anesthesia, Rama Medical college Hospital and Research Center,Pilkhuwa,Hapur, India. Study was conducted from January 2018 toJanuary 2020.Ethical clearance permission for the study was taken from the institutional ethical committee.50 patients ASAphysical status I–II of either sex aged 18 to 60yrs and weighing from 50 to 100 kg anticipated to undergo major abdominal surgery under general

anesthesia were included in this study The anticipated duration of surgery was ≤2 hours.Patients were randomly divided into two groups of 25 patients each to receive one of the following premedication-Group I (Midazolam):Patientsreceived Tab.Midazolam 7.5 mg orally one hour before induction ofanesthesia Group II (Clonidine): Patients receivedTab. Clonidine 100 µg orally, one hour before induction of anesthesia.

SELECTION OF CASES

Patients with any chronic medical illness or respiratory or cardiovascular disease allergic to the drugs (benzodiazapines or clonidine)or NSAID Salcoholic and psychiatric patients were excluded from studyInformed and written consent for participation in the study was obtained from each patient prior to inclusion in the study. A thorough preoperative evaluation of each patient was done.A detailed medical history and a general physical and systemic examination of each patient was performed. All routine laboratory biochemical and hematological tests was done. ECG and X-Ray was obtained.At the time of this checkup, they were familiarized with sedation score.Patients were fasted for 6-8 hrs prior to surgery.All sedative hypnotic premedication were avoided before the surgery.Baseline vitals heart rate,blood pressure, O2, saturation,sedation score before giving premedication was recorded.Tab. Midazolam 7.5 mg or Tab. Clonidine 100 µg orally one hour before induction ofanaesthesia. In the operation room patient was monitored for ECG lead II,Heart RatePulse Oximeter,Non-invasive Blood Pressure (Systolic BP, Diastolic BP and Mean BP). end tidal carbon dioxide, temperature, urine-output,Neuromuscular blockade.Vitals were noted just prior to induction of anesthesia (Pre induction), after intubation (Post intubation), before the surgical incision after the surgical incision (Post incision), and at the end of surgery (End of surgery).Sedation scorebefore induction and after extubation was observed using OAA/S sedation/alertness score.Before induction, patients werepreoxygenated with 100% Oxygen.Anesthesia was inducedwithinj. Propofol 2mg / kg andInj. Fentanyl 2.0 µg / kg.AftergivingInj. Vecuronium bromide 0.1 mg / kgbodywt. IV.andventilating the patient with O2and N2O for 3 minutes,trachea was intubated with cuffed oral endotracheal tube of appropriate size and anesthesia was maintained with Isoflurane Nitrous oxide andoxygen with controlled ventilation to keep EtCO2withinnormal range.Duringmaintenance of anesthesia, administration of Inj Fentanyl 0.5 to 1 µg / kg body wt. was added depending upon clinical condition like (movement, swallowing, lacrimation, sweating,) and alteration of hemodynamic parameters like, a 20 % increase in the systolic blood pressure or heart rate from the base line values. At the end of the surgery neuromuscular blockade was reversed with Inj. Neostigmine (0.04 mg/kg) and Inj. Glycopyrrolate (0.01 mg/kg). At the end of the surgery, all patients were given inj. Ondensetron 4 mg for prevention of PONV. Post operatively patients were kept in post anaesthesia care unit (PACU). Time to achieve full Aldret score was noted for patient to be ready to be shifted from PACU.

OBSERVATIONS AND RESULTS

By using 2 independent sample t-test p-value > 0.05 therefore there was no significant difference between Group midazolam and Group clonidine with respect to demography.

By using 2 independent sample t-test p-value > 0.05 therefore there was no significant difference between Group clonidine and Group control with respect to type of surgical procedures performed.

There was statistically significant difference seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to HR from baselineb- Pre-Induction, c-After Intubation, d-Before incision, e- After incision, f -End of Surgery g-At aldret score of 10. There was significant attenuation of heart rate in clonidine group as compared to midazolam group.

There was statistically significant difference seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to BP from baselineb- Pre-Induction, c-After Intubation, d-Before incision, e- After incision, f -End of Surgery, g-At aldret score of 10. There was significant attenuation of blood pressure in clonidine group as compared to midazolam group

There was statistically insignificant (2 independent sample t-test p-value > 0.05)difference seen between Group 1 (midazolam) and Group 2 (clonidine)with respect to O2saturation. None of the group desaturated at any point of time.

There was statistically significant difference (p value <0.001) seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to sedation score from baseline, Pre-Induction and post operatively. Clonidine group patients were more sedated ascompared to midazolam group.

There was statistically significant (p value<0.001) difference seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to opioid /analgesic requirement. Opioid requirement was morein midazolam group as compared to clonidine group.

There was statistically significant (p value<0.001) difference seen between Group 1 (midazolam) and Group 2 (clonidine) with respect to aldret score. Full Aldret score achieved earlier in midazolam group as compared to clonidine group.

Table 1: Demographic characteristics of patients

	Group1	Group2	P value
Age	37.92±10.57	38.16±11.07	0.938
Weight	63.96 ±10.01	62.96 ± 8.93	0.711
SexM/F	12/13	12/13	1
Duration of surgery	54.92 ± 10.31	56.04 ± 9.39	0.690
ASA(I/II)	13/12	13/12	1

Table 2: Surgical Procedures Performed

Type of Surgery	Group1		Group2		P value
	Frequency	%	Frequency	%	
Lap cholecystectomy	2	8%	2	8%	1.000
PCNL	2	8%	3	12%	0.637
Hysterectomy	2	8%	6	24%	0.123
Lap hernia	1	4%	0	0%	0.312
Laparohysteroscopy	3	12%	2	8%	0.637
Laparotomy	5	20%	3	12%	0.440
Liposuction	1	4%	0	0%	0.312

Myomectomy	1	4%	0	0%	0.312
Nephrectomy	3	12%	4	16%	0.684
Ovarian cystectomy	3	12%	2	8%	0.637
Umbilical hernia repair	2	8%	3	12%	0.637
Total	25	100%	25	100%	

Table 3: Comparison of Heart Rate in Group 1(midazolam) and Group 2 clonidine

HR	Group 1		Group 2		P value
	Mean ± SD	Min -Max	Mean ± SD	Min -Max	
HRa	84.20 ± 4.02	78 - 92	81.84 ±4.77	72 - 88	0.065
HRb	80.72 ± 4.33	72 - 88	68.72 ± 2.17	64 - 72	<0.001
HRc	85.84 ± 3.87	80 - 94	72.36 ± 4.02	64 - 81	<0.001
HRd	83.64 ± 4.10	75 - 89	67.60 ± 3.11	62 - 77	<0.001
HRe	85.40 ± 3.45	80 - 90	72.24 ± 3.90	67 - 84	<0.001
HRf	86.64 ± 2.75	81 - 92	72.56 ± 3.67	68 - 82	<0.001
HRg	84±4.33	77 - 92	81.84 ±4.77	72 - 88	<0.001

Table 4: Comparison of Mean Blood Pressure in Group 1(midazolam) and Group 2 clonidine

MBP	Group 1		Group 2		P value
	Mean ± SD	Min -Max	Mean ± SD	Min -Max	
MBPa	86.60 ± 4.73	78 - 96	85.64 ±5.29	77 - 95	0.174
MBPb	84.16 ± 4.16	75 - 90	72.60 ± 2.84	67 - 77	<0.001
MBPc	86.20 ± 4.29	77 - 92	74.00 ± 2.58	70 - 78	<0.001
MBPd	83.48 ± 4.18	75 - 90	71.84 ± 2.69	67 - 77	<0.001
MBPe	85.32 ± 3.85	77 - 91	73.36 ± 3.32	70 - 78	<0.001
MBPf	85.04 ± 4.01	75 - 91	73.20 ± 2.08	68 - 77	<0.001
MBPg	86.50 ±4.762	77 - 95	84.64 ±5.21	76 - 94	<0.001

Table 5: Comparison of O2saturation in Group 1(midazolam) and Group 2 clonidine

SPO2	Group 1		Group 2		P value
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
SPO2a	100.00 ± 0.00	100 - 100	100.00 ± 0.00	100 - 100	-
SPO2b	99.88 ± 0.44	98 - 100	99.64 ± 0.76	98 - 100	0.178
SPO2c	100.00 ± 0.00	100 - 100	100.00 ± 0.00	100 - 100	-
SPO2d	100.00 ± 0.00	100 - 100	100.00 ± 0.00	100 - 100	-
SPO2e	100.00 ± 0.00	100 - 100	100.00 ± 0.00	100 - 100	-
SPO2f	100.00 ± 0.00	100 - 100	100.00 ± 0.00	100 - 100	-
SPO2g	100.00 ± 0.00	100 - 100	100.00 ± 0.00	100 - 100	-

Table 6: Comparison of Sedation score in Group 1(Midazolam) and Group 2 (clonidine)

Sedation Score	Group 1		Group 2		P value
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
Preop	13.68 ±1.03	12 – 15	11.48 ± 1.12	10 - 14	<0.001
Postop	14.00 ± 0.91	12 – 15	12.20 ± 1.00	10 - 14	<0.001

Table 7-Comparision of intraopopiod given in Group 1(Midazolam) and Group 2 (clonidine)

Intra operative opioid given	Group 1		Group 2		P value
	Frequency	%	Frequency	%	
Not Given	0	0%	18	72%	<0.001
Given	25	100%	7	28%	
Total	25	100%	25	100%	

Table 8: Comparison of time to achieve full aldret score in Group 1(midazolam)

	Group 1		Group 2		P value
	Mean ± SD	Min -Max	Mean ± SD	Min -Max	
Aldret Score	44.40 ± 13.25	20 - 75	60.00 ±13.77	40 - 90	<0.001

DISCUSSION

Sedation and anxiolysis are the essential components of anaesthesia for patients before undergoing surgery. Currently, the most commonly used sedative premedicants in the preoperative holding area is midazolam (85%), followed by ketamine (4%), fentanyl (3%), and meperidine (2%).Clonidine, α2–adrenergic agonist is apreanaesthetic agent and hence has been compared with midazolam, the most common premedication used in children.In our study we found that clonidine group patients were more sedated,calm and less anxious than midazolam group. We found that mean OAA/S sedation score in clonidine group was (11.48 ± 1.12) than in midazolam group13.68 ±1.03 withsignificant difference ofp value (p<0.001). Our finding matcheswith the study ofSequeira Trevor et al [10]in 2012 who comparedoral clonidine and oral midazolam in pediatric patients and found that at the time of venepuncture, 33.3% of children belonging to the clonidine group were adequately sedated compared to 23.3% in the midazolam group with a *P* value of <0.05.At the time of mask application, 26.6% of children belonging to the clonidine group were adequately sedated compared to 20.0% in the midazolam group with *P* value of <0.05.Jianping Cao, Xueyin Shi et al [11]in 2009 compared oral midazolam 0.5 mg/kg , clonidine(C2)2μ g/kg & clonidine (C4)4μg/kg andfoundsedation score, parental separation and mask acceptance were significantly higher in clonidine2μ g/kg andclonidine 4μg/kg as compared to midazolam group($p < 0.05$) but sedation was significantly better in group C4 than in group C2 ($p < 0.05$)Leandro Gobbo Braz, M.Det al [12] in 2002 comparedsedation levels of oral preanesthetic clonidine , midazolam and placebo in clinical and electroencephalographic bispectral analysis. There was significant difference among groups in sedation scale. Clonidine and midazolam group were found to have more sedation scale than placebo.However, there were no significant differences in respiratory, hemodynamic and temperature parameters. In our study there was

significant difference seen between midazolam group and clonidine group with respect to haemodynamics(heart rate & mean blood pressure) from baselinebefore induction, after intubation, before incision, after incision and at the end of Surgery. There was significant ($P < 0.05$) attenuation of hemodynamic response to intubation, surgical stress response and extubation with clonidine as compared to midazolam. There was no episode of bradycardia or hypotension at any point of time in any of the group. This was similar to the findings of V. J. Ramesh, et al [13]in 1997 whofound that Clonidine 3 mcg/kgproducedsignificant ($P < 0.01$) attenuation of hemodynamic response to intubationas compared to diazepam0.2mg/kg. Clinically significant hypotension and bradycardia were not observed in any of the patients. Shivinder Singh and Kapil Arora et al [14]compared oral clonidine with placebo in patient undergoing laparoscopiccholecystectomy and found thatperioperatively the mean heart rate was lower in clonidine groupas compared to placebo group. Mean heart rate ranged from 79.28 ± 9.50 to 85.84 ± 10.12 in clonidine group, whereas it ranged between 83.80 ± 12.76 to 100.04 ± 12.16 in placebo group. Perioperatively, the MAP was lower in clonidine group as compared toplacebo group. MABP ranged from 88.77 ± 7.99 to 102.41 ± 10.35 inclonidine group , whereas it ranged from 96.99 ± 6.37 to 114.8 ± 14.08 in midazolamgroup.There was a significant difference seen between midazolam group and clonidine group with respect to opioid/analgesic requirement. Clonidine group required less opioid /analgesicperioperatively as shown by alteration of hemodynamic parameters, like a 20 % increase in the systolic blood pressure or heart rate from the base line values. Katsuya Mikawa, MD,et al [15] studiedthe effect of oral clonidine given preoperatively on postoperative pain in children undergoing minor surgeries. Clonidine 4 µg/kg provided lower objective pain scale (OPS) scores during 12hrs post operatively and reduced requirement for supplementary analgesic.In our study, there is statistically significant difference seen between midazolam and clonidine with respect to time to achieve adequate Aldret score in postop for PACU discharge. Recovery in clonidine group took slightly longer time 60.00 ± 13.77min as compared to midazolam group 44.40±13.25 min.Waldemar Machała et al[16]in 2010compared anaesthetic requirements in patients receiving150 µg of clonidine, 7.5 – 15 mg of midazolam or placebo as premedication. Recovery time was shortest in the placebo group ($p<0.05$), slightly longer in the clonidine group ($p>0.05$), and longest in the midazolam group ($p<0.05$). There was less postoperative adverse effect in clonidine group as compared to midazolam group.Kumkum Guptaet al[19] compared between oralpregabalin, clonidine and placeboand found that were no differences between the groups with respect to awakening and recovery times. They were well oriented and were able to obey commands in the postoperative care unit. Postoperative analgesic need was much less with pregabalin, and clonidine group as compared with control. No significant complication has occurred was seen after use of oral premedication with pregabalin and clonidine. Postoperative nausea and vomiting& shivering were not found in any group.BergendahlHT, et al [17]compared clonidine with midazolam as premedication in children undergoing adeno-tonsillectomy and found no episode of shivering was observed in the clonidine group but was present in five of the patients in the midazolam group ($P = 0.057$). In younger children (< 5 years) the incidence of postoperative confusion was lower in the clonidine group ($P = 0.001$). No difference in the frequencies of PONV incidences. Dahmani S, Brasher C et al[18] in 2010 found that premedication with clonidine was superior to benzodiazepines . Clonidine decreased the incidence of emergence agitation (OR=0.25

[0.11, 0.58]) and produced a more effective early post-operative analgesia (OR=0.33 [0.21, 0.58]).Thus, clonidine is finding its way in anaesthesia practice and its safety and efficacy as a preanaesthetic agent has been reasonably well established.

CONCLUSION

Premedication with 100 micrograms of oral clonidine in ASA I and II patients has been found to be relatively safe and effective method to provide stable hemodynamicsintra-operatively in response to stress of anesthesia and surgery.Sedation was more in clonidine group as compared to midazolam preoperatively and post operatively.Opioid consumption was also less with clonidine as compared midazolam.Oral clonidine premedication also offers additional advantage of reduction of postoperative complications such as pain, nausea-vomiting, and shivering.Although time to achieve adequate aldret score was slightly more in clonidine group.Hence 100 micrograms of oral clonidine can reasonably be recommended as premedication for all surgeries in otherwise healthy adult patients. However further studies are necessary to find out its efficacy in elderly and ASA III and IV patients, particularly in compromised cardiovascular function.

BIBLIOGRAPHY

1. Egan KJ, Ready LB, Nelssy M, Greer BE. Self administration of midazolam for postoperative anxiety: a double blinded study. Pain. 1992; 49:3-8.doi: 10.1016/0304-3959(92)90180-J. PMID-1594280
2. Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: a comparison of four routes of administration. PaediatrAnaesth. 2002;12:685-689. doi:10.1046/j.1460-9592.2002.00918.x.PMID; 12472704
3. Buffett-Jerrott SE, Stewart SH, Finley GA, LoughlanHL. Effects of benzodiazepines on explicit memory in a paediatric surgery setting. Psychopharmacology (Berl).2003;Aug:168(4):377-86.doi 10.1007/s-00213-0031-1429-7.EPub-2003,Jul-4 PMID-12845417
4. McCluskey A, Meakin GH. Oral administration of midazolam as a premedicant for paediatric day-case anaesthesia. Anaesthesia 1994; Sep 49(9): 782–5.Doi:10.1111/J.1365-2044.1994.tb04451.x. PMID 7978134
5. Bergendahl H, Lönnqvist P, Eksborg S. Clonidine: an alternative to benzodiazepines for premedication in children. CurrOpinAnaesthesiol. 2005Dec; 18(6):608-13.doi 10.1097/01.aco.0000191891.44314.36 PMID16534300
6. Bergendahl H, Lönnqvist P, Eksborg S. Clonidine in paediatric anaesthesia: review of the literature and comparison with benzodiazepines for premedication.Acta Anaesthesiol Scand. 2006(2); 50:135-143doi 10.1111/j.1399-6576.2006.00940.x PMID 16430532
7. Bergendahl H, Lönnqvist P, Eksborg S. Clonidine: an alternative to benzodiazepines for premedication in children. CurrOpinAnaesthesiol. 2005; 18:608-613.
8. Inomata S, Kihara S, Yaguchi Y, Baba Y, Kohda Y,Toyooka H. Reduction in standard MAC and MAC for intubation after clonidine premedication in children. Br J Anaesth. 2000; 85:700-704.doi.org/10.1093/bja/85.5.700

9. Kain ZN, Mayes L, Bell C, Weisman S, Hofstadter M, Rimar S. Premedication in the United States: a status report. AnesthAnalg1997;84:427–32.doi-10.1097/00000539-199702000-00035
10. Sequeira Trevor, Madhusudan Upadya, Chandni Sinha, and Manpreet Kaur.A comparison of midazolam and clonidine as an oral premedication in pediatric patients Saudi J Anaesth. 2012 Jan-Mar; 6(1): 8–1doi 10.4103/1658354x.93045.ISSN:1658354x
11. Jianping Cao Xueyin Shi2, Xiaoyong Miao, Jia Xu. The effects ofpremedication of midazolam or clonidine onperioperative anxiety and pain inchildren BioScience Trends. 2009; 3(3):115-118, ISSN- 18817815
12. Leandro Gobbo Braz, Pedro ThadeuGalvão Vianna, José Reinaldo CerqueiraBraz, Maria ZoéTurchiari de Mello, Lídia Raquel de Carvalho. Sedation levels of oral preanesthetic clonidine and midazolam. Clinical and electroencephalographic bispectral analysis.RevistaBrasileira de Anestesiologia(2002).
13. Ramesh VJ, Bhardwaj N, Batra YK. Comparative study of oral clonidine and diazepam as premedicants in children. Int J Clin PharmacolTher1997;35:218–21doi 10.18535/jmscr/v5i6.125, ISSN-09461965
14. Shivinder Singh and Kapil Arora. Effect of oral clonidine premedication on perioperative haemodynamic response and post-operative analgesic requirement for patients undergoing laparoscopic cholecystectomy. IndianJ Anaesth. 2011 Jan-Feb; 55(1): 26–30doi 10.4103/0019-5049.76583, ISSN-00195049
15. Katsuya Mikawa,KahoruNishina, Nobuhiro Maekawa, andHidefumiObara. Oral Clonidine Premedication Reduces Postoperative Pain in Children. Pediatric anesthesia.1996 Feb;82(2)225-230.doi 10.1097/00000539-199602000-00001, PMID-8561317
16. Waldemar Machała.Effects of clonidine and midazolam on anaesthetic requirements2010, Anaesthesiology Intensive Therapy; 113-116AnestejolIntens Ter (2010).
17. Bergendahl H, Lönnqvist P, Eksborg S, Ruthström E,Nordenberg L, Zetterqvist H, Oddby E. Clonidine vs.midazolam as premedication in children undergoing adenotonsillectomy: a prospective, randomized,controlled clinical trial. Acta Anaesthesiol Scand. 2004;48:1292-1300. Doi 10111/j1399-6576.2004.00525.x.
18. Dahmani S, Brasher C, Stany I, Golmard J, Skhiri A, Bruneau B, Nivoche Y, Constant I, Murat I.Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies.Acta Anaesthesiol Scand.2010 :397-402.doi 10111/j1399-6576.2009.02207.x, ISSN-00015172
19. Kumkum Gupta, Deepak Sharma and Prashant K. Gupta. Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopiccholecystectomy: A comparative study evaluation Saudi J Anaesth2011 Apr-Jun;5(2): 179-184.doi 10.4103/1658-354x.82791.PMID -21804800