EFFICACY OF ORAL CLONIDINE AS A PREMEDICANT IN PAEDIATRIC ADENOTONSILLECTOMY IN COMPARISON WITH ORAL DIAZEPAM

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ABSTRACT: This prospective clinical study was conducted at Government General Hospital, Chennai in patients aged 7-12 yrs undergoing adenotonsillectomy. After approval of hospital ethical committee for the study, informed consent was obtained from the parents. A double blinded randomized, comparative parallel group design was employed. Eighty ASA I patients of both sexes aged 7-12 years undergoing adenotonsillectomy surgeries were studied in this clinical trial. These patients were randomly allocated to two groups of 40 each – Group C received T. Clonidine 4µg/kg while Group D received T. Diazepam 0.15mg / kg as premedication 90 minutes prior to surgery with sips of water. Preoperative sedation and anxiety, hemodynamic changes during laryngoscopy, intubation and during the procedure were assessed. Post operative pain scores were recorded every half-an-hour for the first 4 hours after extubation. The data obtained were subjected to statistical analysis. Z test was applied. P value < 0.05 was considered statistically significant. The demographic profile was comparable in both the groups. Preoperative sedation and anxiety relief was statistically significant in Group C ($P<0.05$), Stable hemodynamic were observed in Group C throughout the procedure. None of the patients in Group C required intervention for bradycardia or hypotension. Significant post operative analgesia was noted in Group C (97.5%) as compared to Group D (10%) even after 4 hours. Children in neither group had respiratory complications post operatively. Oral clonidine in the dose of 4µg/kg is an effective analgesic and sedative for children undergoing adenotonsillectomy in age group of 7-12 years.

KEY WORDS: Clonidine, Diazepam, Adenotonsillectomy

INTRODUCTION: Older children are the group for whom premedication is still most often administered. Premedication in children is used to provide sedation and anxiolysis before surgery, easy separation from parents, and acceptance of intravenous cannulation. It should also provide an optimal intubating condition and stable hemodynamic along with an adequate depth of anaesthesia. An ideal premedicant should be effective orally, a potent analgesic and non-emetic. In should minimize the dose of induction agents and not to impair the cardiovascular stability or respiration.

Many oral premedication cocktails have been found to be safe when properly administered and will not delay discharge after outpatient surgery (1, 2). Intra nasal and oral (lollipop) administration of narcotics (Fentanyl, sufentanil) (3, 4) - though they reduce perioperative analgesic requirements, they have also been associated with complications like chest rigidity and delayed emergence with higher doses. Oral, rectal and nasally administered midazolam has also been used in children to keep them calm and happy (5, 6, 7).

Clonidine has been chosen as a premedicant to assess the preoperative sedation, anxiety, intraoperative hemodynamic stability and post operative analgesia in comparison with diazepam. The complication of clonidine if any when used as a premedicant was also evaluated.

METHODS: Eighty ASA I patients of both sexes aged 7-12 years were randomly allocated to one of the two groups-Groups C and D Group C received Tab. Clonidine 4 µg/kg and Group D received T. Diazepam 0.15 mg/kg as premedication 90 minutes prior to surgery.

All the children were subjected to routine biochemical investigations, ECG and Chest roentgenogram after admission to the hospital. Preoperative anaesthetic assessment was performed.

On arrival to the operating room, baseline heart rate and blood pressure were noted prior to premedication. Patient's saturation was monitored with pulse oximeter. Oxygen was to be supplemented with mask if saturation dropped below 90%. Heart rate and blood pressure were recorded 60 minutes and 90 minutes after premedication and just prior to induction of anaesthesia. The children were assessed for the level of sedation and anxiety by using sedation and anxiety scales respectively.

Sedation Scale [8]	**Anxiety Scale** [8]	
Grade I - Awake and alert		
Grade II - Awake, Calm, lying down quietly.	Grade 1	-Combative
Grade III - Drowsy, arousable on oral command.	Grade 2	-Tearful
Grade IV - Drowsy, arousable on mild physical stimulus	Grade 3	-Apprehensive
Grade V - Asleep, sedated, arousable on vigorous physical stimulus	Grade 4	-Calm

In the operating room after obtaining intravenous access and connecting the monitors, Inj. Glycopyrrolate 0.1 mg was given. Fluids were calculated for starvation and maintenance according to the body weight (4-2-1 rule). Dextrose half normal saline was started and maintained with ringer lactate.

Induction was performed with 5 mg/kg of 2.5% thiopentone sodium, Inj Fentanyl 2 µg/kg and Injection atracurium 0.5mg/kg. After two minute of mask ventilation with 100% Oxygen, laryngoscopy was performed and the children were intubated orally with appropriate sized endotracheal tubes. Anaesthesia was maintained with 66% Nitrous oxide in oxygen. Heart rate and blood pressure were recorded at 1, 2,4,6,8 and 10 minutes after intubation and then intermittently throughout the procedure. Incremental top up doses of atracurium were given according to surgical relaxation requirements. Anaesthetic management was designed to maintain heart rate within 25% and arterial pressures within 20% limits of baseline values.

Hypotension (>20% reduction of baseline blood pressure) was to be treated by (a) Fluid challenge with 50ml of balanced salt solution (b) 3mg bolus dose of intravenous ephedrine if there was no response to fluid challenge.

Bradycardia (Heart rate<60/min) was to be treated with Inj. Atropine 20 µg/kg increment intravenously.

Hypertension or tachycardia sustained for at least more than 5 minutes was treated by halothane inhalation in 0.5% increment to deepen anesthesia or supplemental fentanyl 0.5 µg/kg if necessary.

Halothane if administered was terminated about 10-15 minutes before reversing the patient. Nitrous oxide was terminated at the moment when the neuromuscular block was being antagonized with atropine 25µg/kg and neostigmine 50 µg/kg.

Patients were then extubated and observed for 10-15 minutes by monitoring the vital signs including respiration. On awakening, assessment of pain was made and it was continued into the post-operative period for four hours using the post-operative pain scale.

Analysis of post-operative pain [8]

Grade I : Patient restless, screaming with pain.
Grade II : Patient complaining of severe pain and demands relief.
Grade III : Patient comfortable, complains of pain on questioning.
Grade IV : No complaint of pain.

At the end of the study, all the data was compiled systematically and analyzed using 'Z' test. Epi info software package was used. P value <0.05 was considered statistically significant.

RESULTS: The patient groups were comparable in distribution of age, sex, ASA status and the baseline hemodynamic values (i.e.) statistically non-significant (P>0.05).

Parameters	**Group C (n=40)**	**Group D (n=40)**
Age (in years)	10.25 (7-12)	10.375 (7-12)
Sex		
Male	21 (52.5%)	17 (42.5%)
Female	19(47.5%)	23 (57.5%)
ASA status	1(100%)	1(100%)
Baseline values		
Heart rate (beats/min	99.5(80-120)	101.88 (85-124)
Blood pressure (mm/Hg)	108(90-120)	107.5 (100-130)
Systolic/Diastolic	71 (60-80)	69.75 (60-80)

Table 1: Demographic Characteristics

(p>0.05)

There was a significantly higher degree of sedation in Group C (i.e.) 70% were under grade III while 87.5% in Group D were under Grade I. Statistical significance p<0.05

Degree of Sedation	I	II	III	IV	V
Group C (N= 40)	0	10	28	2	0
Group D (N=40)	35	4	1	0	0

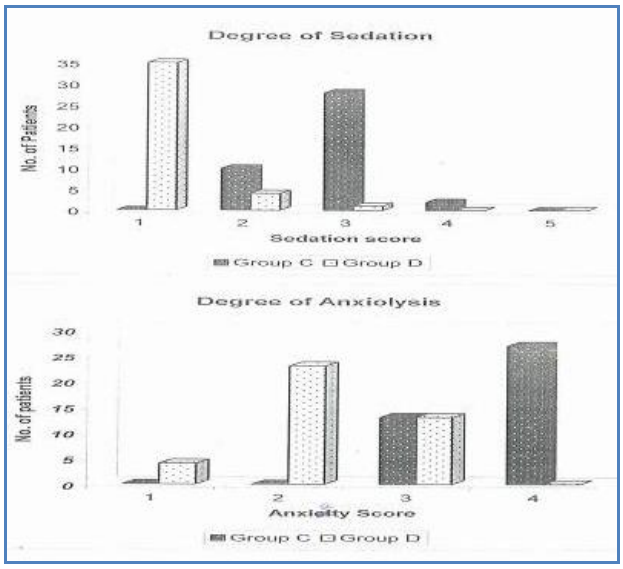
Table: 2

Statistical significance (p<0.05) was noticed between the groups considering grade 3 & 4 anxiety scores.

Anxiety score	1	2	3	4
Group C (n= 40)	0	0	13	27
Group D (N=40)	4	24	13	0

Table: 3

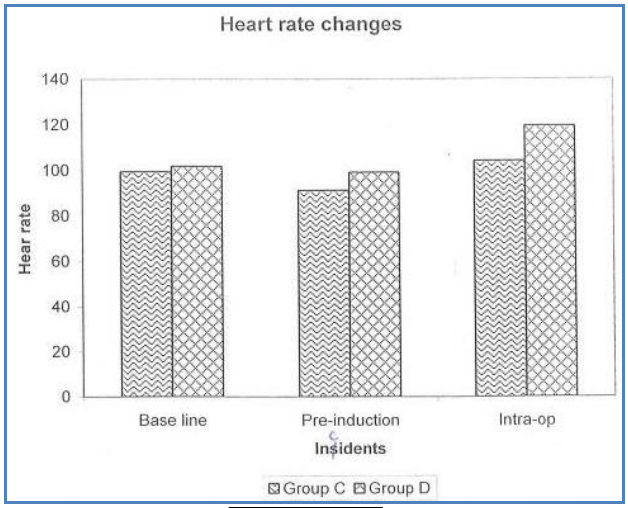
The increase in the heart rate associated with laryngoscopy and tracheal intubation was attenuated significantly in group C as compared to group D. Patients in group C also had a statistically significant lower heart rate and pressure values during the surgery as compared to group D patients (p<0.05).



Graph: 1

	Group C	Group D	
Baseline			
Heart rate	99.5	101.87	
Systolic (SAP)	108	107.5	p>0.05
Diastolic (DAP)	71	69.75	
Intraoperative			
Heart rate	104.5	119.52	
Systolic (SAP)	99	120.75	P<0.05
Diastolic (DAP)	70.65	74.25	

Table: 4



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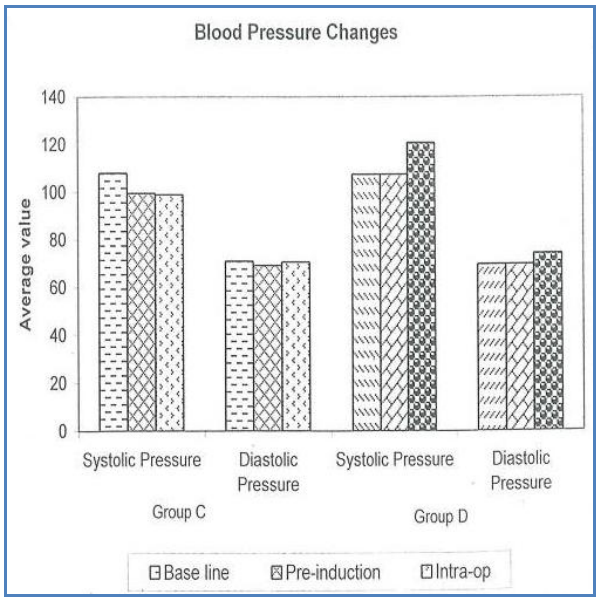
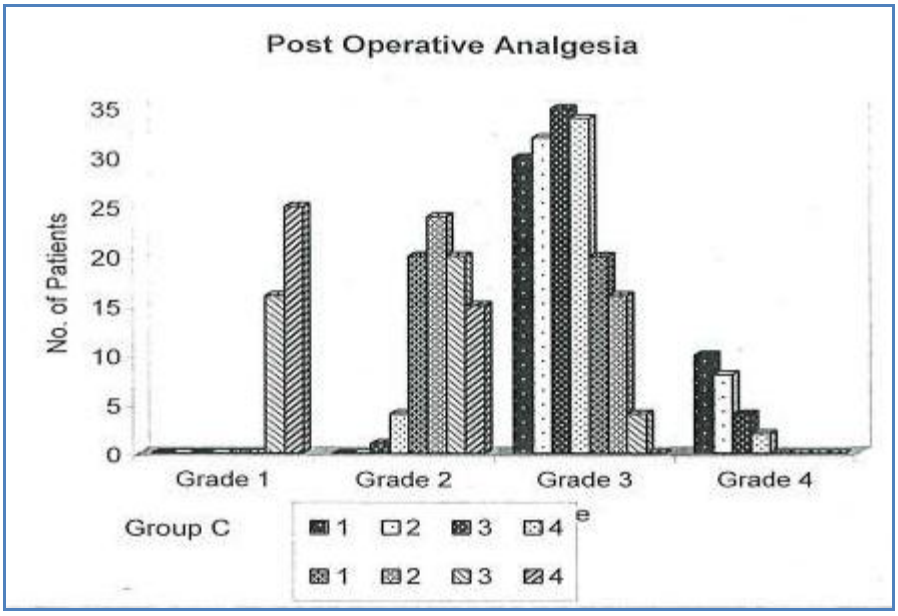
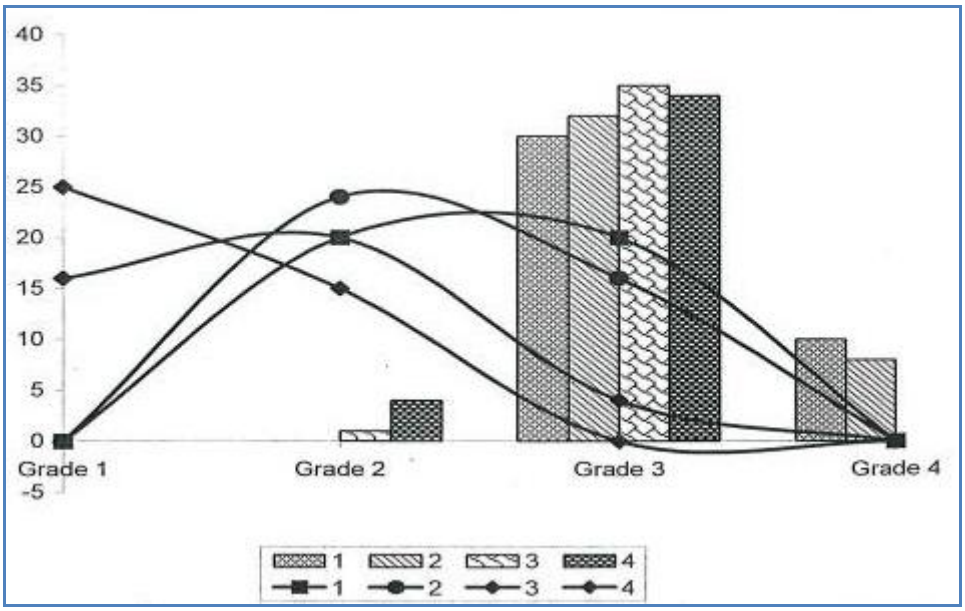


Graph: 3

95% of patients in clonidine group remained in Grade 3 & 4 of postoperative analgesic scale even after two hours after extubation while only 10% in the diazepam group were in grade 3 after two hours requiring analgesic. The analgesia noted in the first two hours after surgery might be attributed to intraoperative fentanyl. Children of clonidine group remained pain free even after two hours.

None of the patients in both the groups had any postoperative problems like vomiting or airway obstruction.





Graph: 4

DISCUSSION: The selected goals for premedication according to Tinker and Morgan (9) are relief of apprehension, sedation, analgesia, amnesia, to prevent undesirable side effects and autonomic reflex responses, to decrease MAC of volatile anaesthetics, to facilitate anaesthetic induction, anti sialagogue effect, to prevent nausea and vomiting and to reduce gastric fluid volume and acidity.

Children above 6-12 months may benefit from sedative hypnotic drug before surgery. Oral premedication is used in older children (10). In children more than 3 years of age drugs may be given rectally or nasally. Diazepam and Pentobarbital given orally has become less popular due to its long half life. Though midazolam produces fewer behavioral disturbances it is expensive comparatively.

Methohexital (20-30mg/kg) given rectally (11). Oral ketamine in the dose of 6mg /kg is associated with emergence delirium in short procedures (12).

Clonidine, an imidazoline compound is a selective α2 agonist with a ratio of 200:1 (α2: α1) and it is a partial agonist (13). Because of its lipid solubility, it is rapidly and almost completely absorbed after oral administration and its bioavailability is nearly 100%. Peak plasma concentration is reached within 60-90 minutes (14) and its elimination half life is between 9-12 hours. Approximately 50% of the drug is metabolized in the liver to inactivate form while the rest is excreted unchanged by the kidney. It has been administered by the epidural, intravenous, oral and rectal routes in children (15, 16 and 17).

In anaesthetic practice clonidine is used as a premedicant, for intraoperative hemodynamic stability, intrathecal administration to potentiate local anaesthetics and epidural and systemic administration for post operative analgesia (18).

Extradural clonidine (100-900µg) is used for relief of neuropathic pain and also in the management of refractory reflex sympathetic dystrophy. Intrathecal clonidine is used in the attenuation of cancer and terminal pain in morphine resistance patients (18). Other therapeutic uses are as an antihypertensive agent (19) and in the treatment of opioid, alcohol and cigarette addiction and anxiety attacks (20).

Clonidine is an analgesic that acts centrally at the locus coeruleus in the brain stem and locally at the spinal cord [21].

As a non-opioid analgesic, clonidine provides analgesia without opioid side effects, most importantly respiratory depression. It has several additional effects including sedation, decreased salivation, decreased anaesthetic requirement, improved intraoperative hemodynamic stability and decreased vomiting [22, 23].

Adrenergic agonist drugs act at the CNS and presynaptically at the peripheral nerve terminals to cause a reduction in the activity of sympathetic nervous system. This property gives an added advantage to clonidine over any other premedicant in being the drug of choice to attenuate the sympathetic over activity under anaesthesia, thereby providing optimal surgical conditions.

Published paediatric experience with oral clonidine is limited. In a study by Mikawa et al[24], 90 children between 5 and 12 years of age undergoing minor (Ophthalmic, urologic or otologic surgery) were studied. Patients were randomly allocated into three groups receiving a placebo, clonidine 2 μg/kg or clonidine 4μg/kg as premedication 105 minutes prior to induction. They found that clonidine 4μg/kg provided better preoperative sedation than the other two. Hence in this study, clonidine 4μg/kg was chosen Inj. Glycopyrrolate 0.1 mg was included during induction and no difficulties were encountered with hypotension or bradycardia. The sedation produced by clonidine in this study was comparable to the study by Mikawa et al [24].

Fentanyl was chosen intraoperatively because of its shorter duration of action since adenotonsillectomy was a shorter procedure and patients can also be assessed for postoperative pain and subsequent requirement of analgesics. Children in group D were hemodynamically stable and maintained their heart rate and blood pressure to the baseline values. But none required treatment for hypotension, hypertension, tachycardia or bradycardia. This correlates well with the study by Eleanor et al [8] were 36 children aged 7-12 years undergoing adenotonsillectomy were studied. No incidences of hypotension or bradycardia were reported in their study also. This reduction in the perioperative variations in heart rate and BP may be attributed to the inhibitory action of clonidine on spontaneous as well as evoked activity of the central monoaminergic systems involved in the modulation of nociception, cortical arousal and the sleep / wake cycle mediated by the α2 adrenergic receptors.

Clonidine did not prolong awakening from anaesthesia in this study although it is known to possess sedative properties.

This study limited the observation period to the first four hours postoperatively as this is the time when most doses of analgesics are administered to ensure analgesia and when complications such as airway obstruction become apparent. The prolonged action of clonidine may have been demonstrated if the observation period was continued for 24 hours. A prolonged analgesic effect may be advantageous compared to the shorter acting analgesic effects of intravenous opioid.

Adenotonsillectomy may result in considerable intraoperative blood loss that can be exacerbated by inadequate anaesthetic depth. In addition, extreme agitation during recovery can potentially disrupt the freshly coagulated tonsillar bed and increase the risk of postoperative bleeding.

Oral clonidine has also been investigated as an analgesic in children undergoing minor surgery. A dose of 4 μg/kg was found to reduce objective pain scores and analgesic requirements for

12 hours postoperatively by Mikawa et al [24]. In the study by Eleanor et al [8], no adverse effects were noted by sending the children home after six hours of observation.

Although no children in this study required treatment for bradycardia or hypotension, younger children may require anticholinergic premedication to prevent important bradycardia and decreased cardiac output [25].

SUMMARY: Oral clonidine is an effective analgesic and sedative for children undergoing adenotonsillectomy.

Clonidine in the dose of 4µg/kg has proved to be adequate and free of side effects in children aged 7-12 years.

Clonidine produced significant sedation and anxiolysis in children promoting easy separation from parents and acceptance of intravenous cannulation. It also provided improved hemodynamic stability by attenuating the stress induced sympatho adrenergic responses to anaesthesia and surgery when compared to oral diazepam. Although clonidine has been shown to have hemodynamic side effects, no such incident was seen in this study.

Clonidine also reduced the need for postoperative analgesic in children after adenotonsillectomy.

REFERENCES

1. Brzustowicz RM, Nelson DA, Betts EK et al. Efficacy of oral pre- medication for paediatric out-patient surgery, Anaesthesiology 1984; 60: 475.
2. Nicolson SC, Betts EK, Jobes DR et al. Comparison of oral and intra- muscular pre- anaesthetic medication for paediatric in- patient surgery, Anaesthesiology 1989;
3. Feld LH, Champeau MW, Van Steennis CA et al. Pre- anaesthetic medication in children: A comparison of oral trans- mucosal fentanyl citrate versus placebo. Anaesthesiology 1989; 71: 374.
4. Henderson JM, Brodsky DA, Fisher DM et al. Pre- induction of anaesthesia in paediatric patients with nasally administered Sufentanil, Anaesthesiology 1988; 68: 671.
5. Saarnivaara L, Lindgren L, Klemola UM. Comparison of chloral hydrate and Midazolam by mouth as pre- medicants in children undergoing oto- laryngological surgery. British Journal of Anaesthesia 1988; 61:390.
6. Spear RM, Yaster M, Berkowitz ID et al. Pre-Induction of anaesthesia in children with rectally administered Midazolam. Anaesthesiology 1991; 74:670.
7. Wilton NC, Leigh J. Rosen DR et al. Pre-anaesthetic sedation of pre- school children using intra-nasal Midazolam. Anaesthesiology 1988; 69:972.8:71.
8. Eleanor J. Reimer, Gullian S Dunn, Carolyne J. Montgomery, Peder M. Senderson, Louis D. Scheepers, Pamela M. Merrick, The effectiveness of Clonidine as an analgesic in paediatric adenotonsillectomy. Canadian Journal of Anaesthesia 1998; 45:12, pp 1162-1167.
9. Principles and practice of Anaesthesiology 2nd edition by David E. Longnecker, John H.Tinker, G. Edward Morgan Jr., Page. 53.
10. Principles and practice of Anaesthesiology 2nd edition by David E. Longnecker, John H.Tinker, G. Edward Morgan Jr., Page. 2093.
11. Principles and practice of Anaesthesiology 2nd edition by David E. Longnecker, John H.Tinker, G. Edward Morgan Jr., Page 5.

12. Gutstein HB, Johnson KL, Heard MB et al. Oral ketamine preanesthetic medication in children. Anaesthesiology 1992; 76 : 18.
13. Goodman and Gilman's. The pharmacological Basis of Therapeutics. 8th Edition, 1991, Vol. I pages. 208-209.
14. International Practice of Anaesthesia, Vol. I, Cedric Prys. Roberts and Burnell R. Brown Jr. 1/19/4.
15. Jamali S, Monin S, Begon C, Dubousseta M, Ecoffey C. Clonidine in paediatric caudal anaesthesia. Anesth Analg 1994; 78: 663-6.
16. Bernard JM, Hommeril J- L, Passuti N, Pinaud M. Post- operative analgesia by intra-venous clonidine. Anaesthesiology 1991; 75: 577- 82.
17. Lonnquist PA, Bergendahl HTG, Eksborg S. Pharmacokinetics of clonidine after rectal administration in children. Anaesthesiology 1994; 81:1097-101.
18. Y. Haysashi and M. Maze. 2 adrenoceptor agonists and anaesthesia BJA (1993), 71; 108- 118.
19. International Practice of Anaesthesia, Vol. I, Cedric Prys. Roberts and Burnell R. Brown Jr. 1/19/8.
20. Aantaa R and Scheinin M. α2 adrenergic agents in Anaesthesia. Acta Anaesthesiol Scand 37: 433- 88.
21. Tong C, Eisenach JC, α2 Adrenergic agonists. New drugs in Anaesthesia part II. Anaesthesiology Clinics of North America, Philadelphia. W.B. Saunders, 1994; 12:49-63.
22. Maze M, Tranquillis W. α2 adrenoreceptor agonists: defining the role in clinical anaesthesia. Anaesthesiology 1991; 74: 581-605.
23. Mikawa K, Nishina K, Maekawa N, Asano M, Obara M. Oral Clonidine premedication reduces vomiting in children after strabismus surgery. Canadian Journal of Anaesthesia 1995; 42 : 977-981.
24. Mikawa K, Nishina K, Maekawa N, Obara H. Oral Clonidine premedication reduces post operative pain in children. Anesth Analg 1996; 82: 225- 230.
25. Nishina K, Mikawa K, Maekawa N, Obara H. Oral Clonidine premedication blunts the heart rate response to intravenous atropine in awake children. Anaesthesiology 1995; 82: 1126- 1130.

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