

A COMPARATIVE EVALUATION OF ORAL CLONIDINE, DEXMEDETOMIDINE, AND MELATONIN AS PREMEDICANTS IN PEDIATRIC PATIENTS UNDERGOING SUB-UMBILICAL SURGERIES

Syed T Ali¹, Veena Asthana¹, Divya Gupta¹, Santosh K Singh²

¹Department of Anaesthesiology, Himalayan Institute of Medical Sciences,

Swami Rama Himalayan University, Dehradun, Uttarakhand

²Department of Surgery, Himalayan Institute of Medical Sciences,

Swami Rama Himalayan University, Dehradun, Uttarakhand

Abstract

Introduction: Sedative premedication is the mainstay of pharmacological therapy in children undergoing surgeries. This study compares preoperative melatonin, clonidine, and dexmedetomidine on sedation, ease of anesthesia induction, emergence delirium, and analgesia. **Materials and Methods:** One hundred and five children, 3–8 years, either sex, ASA I/II, posted for infraumbilical surgery, randomized to receive clonidine 5 mcg/kg (Group C), dexmedetomidine 3 mcg/kg (Group D), and melatonin 0.2 mg/kg (Group M) 45 minutes before surgery. Preoperative Sedation/Anxiety and Child-Parent Separation Score (CPSS) were assessed. Identical anesthesia technique was utilized. Emergence delirium (Watcha score) and postoperative pain (Objective Pain Scale score) were monitored postoperatively. **Results:** Patients were demographically comparable. Sedation score >Grade 3 was absent. Grades 1/2/3 were present in 10/19/6 (Group C), 2/26/7 (Group D), and 7/26/2 (Group M). Grade 1 CPSS was present in 42.6% (Group C), 37.1% (Group D), and 28.6% (Group M). Pediatric Anesthesia Behavior Score (PABS) was comparable between Groups C and D ($p = 0.224$; 95% CI -0.090 to 0.604) and Groups C and M ($p = 0.144$; 95% CI -0.633 to 0.061) while PABS was better in Group D compared to Group M ($p = 0.0007$; 95% CI -0.890 to -0.195). Watcha scores were 33/2/0/0 (Group C), 34/1/0/0 (Group D), and 32/2/1/0 (Group M) immediately after extubation. Scores were 31/4/0/0 (Group C), 33/2/0/0 (Group D), and 31/4/0/0 (Group M) at 30 minutes and 28/7/0/0 (Group C), 29/6/0/0 (Group D), and 24/11/0/0 (Group M) at 1 hour. The scores were comparable ($p > 0.05$). Objective Pain Scale scores were comparable between Groups C and D and Groups C and M ($p > 0.05$). Lower scores were present in Group D compared to M ($p = 0.023$). **Conclusion:** Melatonin, clonidine, and dexmedetomidine are efficacious for producing preoperative sedation, reducing anxiety, postoperative pain, and emergence delirium.

Keywords

Premedication • drugs-melatonin • clonidine • dexmedetomidine

INTRODUCTION

Anxiety and fear of unknown and new environment are significant determinants of preoperative agitation in children, manifesting as tearfulness, screaming, clinging to parents, apathy, and withdrawal [1–4]. If not properly handled, its presence is associated with future maladaptive behavior. Incidence of preoperative distress maybe as high as 60%. Sixty percent of children who underwent anesthesia manifest negative behavioral changes upto 2 weeks postoperatively while in 20% of cases these may continue for 6 months [5]. Apart from undesirable effects of sympathetic tone and increased level of catecholamine secondary to stress response, immunological, metabolic, and hormonal changes

also occur [6]. Studies have demonstrated relationship between preoperative anxiety and emergence delirium, increased analgesic requirements, negative behavioral changes, sleep disturbances, and separation anxiety in postoperative period [7]. Uses of pharmacological or non-pharmacological modalities are commonly utilized to decrease preoperative anxiety. Non-pharmacological therapies, though effective, have variable results [8]. Sedative premedicants are the mainstay of pharmacological therapy though different agents and routes of administration have been tried [9]. Non-parental routes like oral/trans mucosal are preferred in children to alleviate the needle fear and pain.

Midazolam has attained a widespread acceptance as a preoperative sedative and an anxiolytic. Use of drugs with

*Corresponding author e-mail: drvasthana@yahoo.co.in

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pharmacological effects other than benzodiazepines has been tried and found to have favorable kinetics. Use of clonidine and dexmedetomidine has been found to have comparable results. Melatonin, a natural hormone produced in brain, has the properties of producing natural sleep and has been used as sedatives in the elderly and children. Few studies have compared the clinical effects of clonidine, dexmedetomidine, and melatonin. With this aim this study was planned to evaluate and compare the clinical effects of α_2 agonists and melatonin on sedation and reduction of anxiety as primary outcome while ease of anesthesia induction, emergence delirium, and postoperative pain as secondary outcome in children undergoing infraumbilical surgeries.

MATERIALS AND METHODS

This randomized observational study was conducted after obtaining Institutional Ethic Committee clearance and written informed consent of parent/guardians. One hundred and five children, between the age of 3–8 years, either sex, ASA status I and II, undergoing elective infraumbilical surgical procedure, were selected. Age >10 years, systemic disease that compromised cardiovascular, respiratory, or neurological function, upper and lower airway disease, known allergy to study drug, history of sleep apnea were excluded from the study. The study was registered retrospectively in ClinicalTrial.gov.in (CTRI/2017/01/007682).

All eligible patients were kept nil per oral for 6 hours for solids and 2 hours for clear fluids. The patients were divided into three groups of 35 each utilizing tables of random number to receive the following drugs: clonidine 5 mcg/kg (Group C), dexmedetomidine 3 mcg/kg (Group D), and melatonin 0.2 mg/kg (Group M). The tablet of melatonin and required dose of injection of clonidine and dexmedetomidine were mixed with syrup paracetamol 2.5 mg/kg and administered orally 45 minutes before surgery. The administration of the drugs was done by DG and she was not responsible for further data collection. Simultaneously EMLA cream was applied over dorsum of hand over proposed site of venipuncture.

The Sedation and Anxiety was assessed before shifting to OR utilizing Ramsay Sedation Score and Child–Parent Separation Score respectively by VA and STA. In the OR after establishing the intravenous access, monitors like ECG, NIBP, and pulse oximetry (Philips Sure Signs VM8) were applied. A bispectral index (BIS) monitor A-2000™ (Aspect Medical Systems, Cambridge, MA, USA) was also attached to all the patients. Induction of anesthesia in all the groups was achieved with injection (inj.) fentanyl 1 mcg/kg and propofol 2.5–3 mg/kg till the BIS value dropped to <50. Mask ventilation was checked and neuromuscular blockade was achieved with inj. atracurium 0.5 mg/kg and intubation was completed

with appropriate sized uncuffed/cuffed endotracheal tube. Anesthesia in all the cases was maintained with 66% nitrous in oxygen, sevoflurane, and intermittent boluses of atracurium and fentanyl to maintain BIS between 40 and 60 and end tidal carbon dioxide of 35–40 mmHg.

Hemodynamic parameters and BIS value were noted at the time of loss of consciousness, 1, 2, and 5 minutes after intubation, and thereafter every 5 minutes till the end of surgery. Inj. paracetamol 15 mg/kg was administered 15 minutes prior to the expected end of surgery. At the end of surgery, sevoflurane and nitrous oxide were switched off and neuromuscular blockade was reversed with neostigmine and glycopyrrolate. The patients were shifted to postanesthesia care unit (PACU) where pain and postoperative delirium were evaluated utilizing Objective Pain scale and Watcha scale at shifting, 30 minutes, 1 hour, 6 hours, 12 hours, and 24 hours after surgery and shifting, 30 minutes, and 1 hour after surgery, respectively.

Data Management: The sample size was calculated on the basis of previous studies [10, 11]. A total of 105 patients were required to detect 20% reduction in anxiety score at 5% level of significance with 80% power of study. The data was statistically analyzed using Microsoft Office Excel 2007 and SPSS (IBM version 22.0). Qualitative data was expressed as frequency and percentage while quantitative data was expressed as mean \pm standard deviation. Kruskal–Wallis H test was used for analyzing sedation score, anxiety score, behavior score, pain score, and emergence delirium score. One-way analysis of variance (ANOVA) was used to analyze hemodynamic variables. Chi-square test was used to study gender and ASA grading in different groups and to compare subparameters of various scales. A p value of <0.05 was considered significant.

RESULTS

One hundred and five patients fulfilling the eligibility criteria were included in the study (Figure 1) between January 2015 and July 2016. All completed the study and there were no dropouts. The children were comparable in terms of demographic profile, type of surgery, and duration of anesthesia and surgery (Table 1).

Preoperative sedation was assessed utilizing Ramsay Sedation Score. None of the children in any group had a sedation score of grade higher than 3. Grades 1/2/3 were seen in 10/19/6 (Group C), 2/26/7 (Group D), and 7/26/2 (Group M).

Child–Parent Separation Score (CPSS) was evaluated on a 4-point scale. Grade 1 of CPSS was considered good while Grades 2, 3, and 4 were considered unsatisfactory for statistical comparison. The grades of CPSS among different

groups were comparable and statistically insignificant (Table 2).

Comparison of sedation with ease of induction was depicted by Pediatric Anesthesia Behavior Score (PABS). PABS was evaluated on a 3-point score as shown in Table 3. For statistical comparison, Grade 1 of PABS was considered as good while Grades 2 and 3 were considered fair to poor. PABS was comparable between Groups C and D ($p = 0.224$; 95% CI -0.090 to 0.604) and Group C and M ($p = 0.144$; 95% CI -0.633 to 0.061). Compliance to induction was better in Group D compared to Group M ($p = 0.0007$; 95% CI -0.890 to -0.195).

Induction dose of propofol was comparable and statistically insignificant ($p > 0.05$). Pain on injection of propofol manifesting as sudden jerky movement of hand was seen in four patients (Group M) and two each in Groups C and D (Table 4).

Perioperative hemodynamic variability is shown in Figures 2 and 3, which was comparable and statistically insignificant ($p > 0.05$). Dexmedetomidine, however, was superior to other drugs for attenuation of response to laryngoscopy and intubation. A significant fall in pulse rate was observed in Group D at preinduction, post induction, and post intubation at 1, 2, and 5 minutes, respectively ($p < 0.05$). Other hemodynamic variables including mean arterial pressure, oxygen saturation, and BIS were stable and comparable among the groups.

Objective Pain Scale (OPS) score is the sum of scores of five parameters: arterial pressure 0: 10% increase from preoperative value, 1: >20% of preoperative value, 2: >30% of preoperative

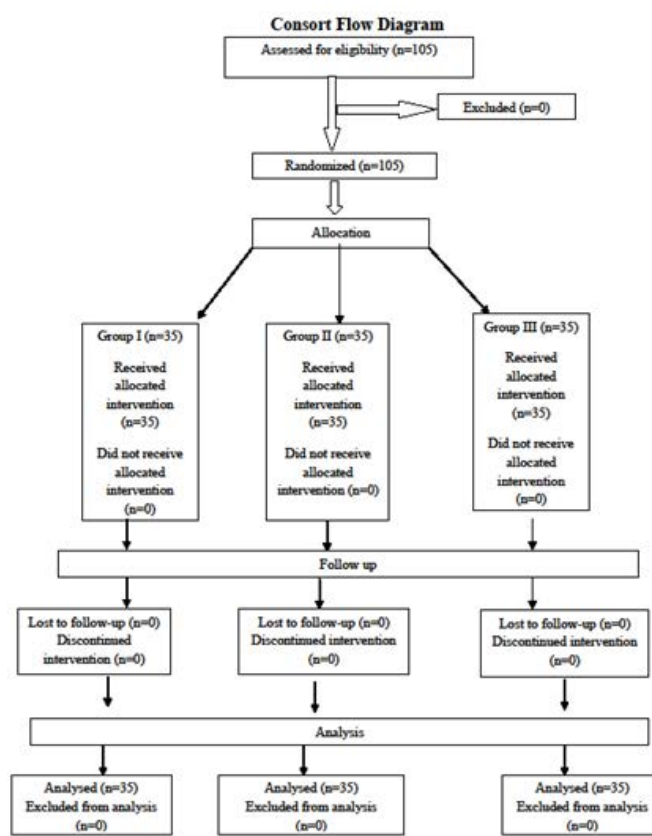


Figure 1: CONSORT Flow Diagram

Table 1. Demographic profile and surgery variables

	Group C (n=35)	Group D (n=35)	Group M (n=35)	P value
Age in years (Mean \pm SD)	4.08 \pm 1.74	4.23 \pm 1.76	4.06 \pm 1.50	0.89 [#]
Gender(M:F)	29:6	30:5	32:3	0.56 [*]
ASA I:II	31:4	32:3	30:5	0.75 [*]
Weight(kg) (Mean \pm SD)	16.11 \pm 6.67	16.50 \pm 6.71	15.02 \pm 4.85	0.58 [#]
Type of Surgery				
Inguinal hernia	15	14	21	
Hypospadiasis	12	13	14	
Anal warts	1	0	0	
Undescended testes	2	2	0	
Subumbilical lump	1	0	0	
Urethral stricture	0	1	0	
Syndactyl digit	1	0	0	
Hydrocele	2	1	0	
#lipoma thigh	1	1	0	
Facitis thigh	0	1	0	
phimosis	0	2	0	
DoA(min) (Mean \pm SD)	97.42 \pm 33.52	107.85 \pm 42.98	95.80 \pm 35.60	0.35 [#]
DoS(min) (Mean \pm SD)	80.71 \pm 30.65	90.00 \pm 41.08	76.71 \pm 31.59	0.26 [#]

One way Anova, *Chi square test, DoA Duration of anaesthesia, DoS Duration of Surgery

Table 2. Child parent separation score (CPSS) among groups

CPSS Grade	Group C (n=35)	Group D (n=35)	Group M (n=35)
1-patient unafraid, cooperative and asleep	15(42.9%)	13(37.1%)	10(28.6%)
2- slight fear or crying, quiet with reassurance	13(37.1%)	21(60%)	17(48.6%)
3- moderate fear, crying, not quiet with reassurance	3(8.6%)	1(2.9%)	5(14.3%)
4crying,need restraint	4(11.4%)	0(0.0%)	3(3.8%)

Group C Vs Group D p=0.808*
 Group C Vs Group M p= 0.318*
 Group D Vs Group M p= 0.611*
 * Chi square test

Table 3: Paediatric Anaesthesia Behaviour Score (PABS) among group

PABS	Group C (n=35)	Group D (n=35)	Group M (n=35)
1: Calm, controlled, compliant with induction	18	24	10
2: tearful, withdrawn but compliant with induction	14	11	20
3: loud vocal resistance/physical resistance to induction, requires physical restraint	3	0	5

Group C Vs Group D p=0.224 (95% CI -0.090 - 0.604)*
 Group C Vs Group M p=0.144 (95% CI -0.633 - 0.061)*
 Group D Vs Group M p=0.0007 (95% CI -0.890 - -0.195)*
 *PostHoc Test

Table 4: Dosage of Propofol

	Group C (n=35)	Group D (n=35)	Group M (n=35)	P value
dose of Propofol (mg) (Mean ±SD)	54.28± 19.10	55.85 ± 20.66	55.57 ± 18.58	0.93#
Pain on Injection	2	2	4	0.58*

One way Anova; *Chi square test

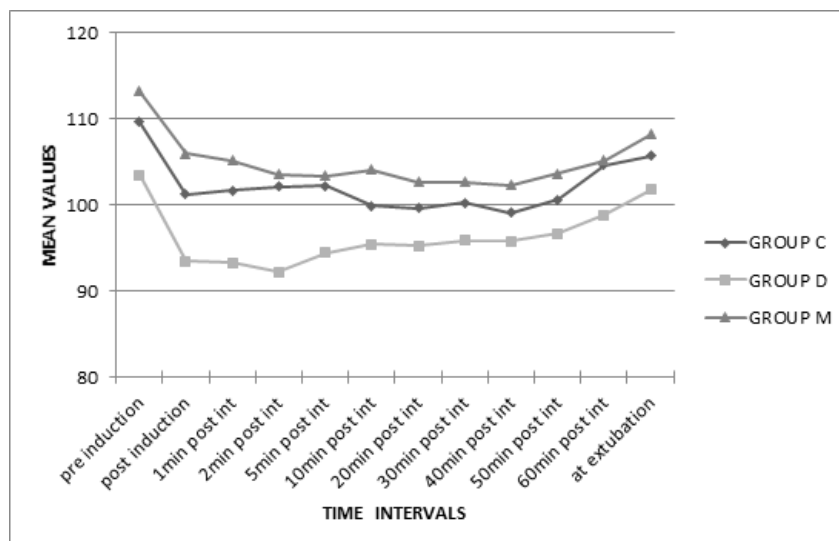


Figure 2: Heart rate at different time intervals among the groups

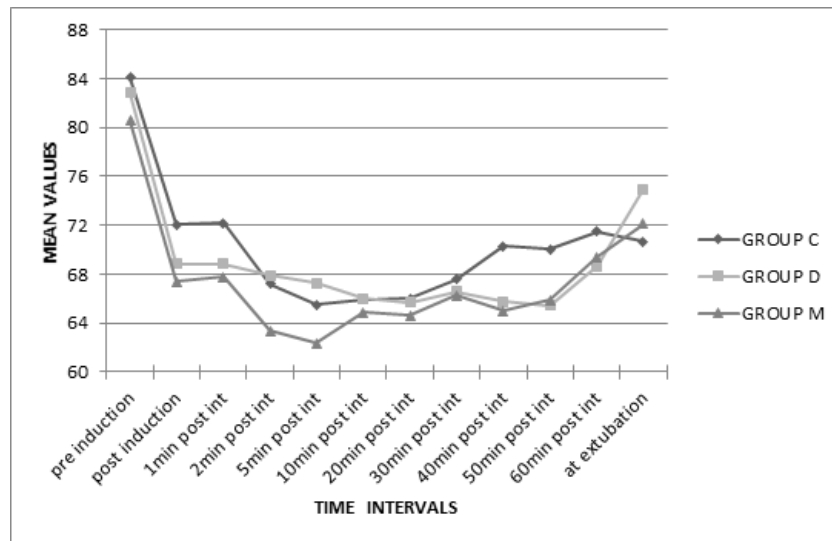


Figure 3: Mean blood pressure at different time intervals

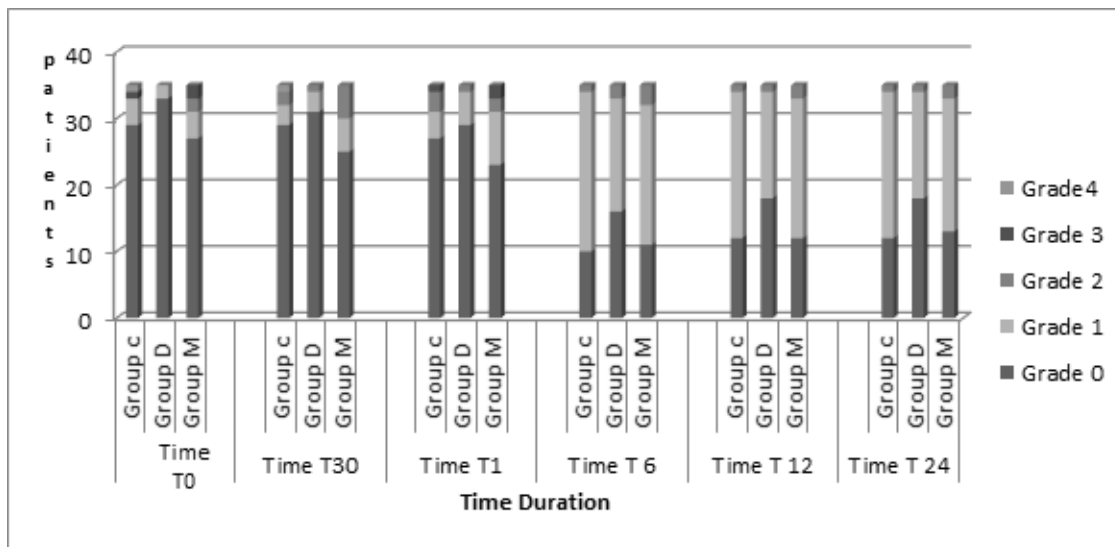


Figure 4: Objective Pain Scale in postoperative period. (OPS scale parameters- arterial pressure, tears, movements, behaviour, verbal or bodily expression, each has score 0,1,2. OPS score is sum of scores of all 5 parameters. Arterial pressure, 0: 10% increase from preoperative value, 1:>20% of preoperative value, 2: >30-% of preoperative value. Tears 0: absent, 1: present but consolable, 2: present and unconsolable. Movements 0: absent,1: moderate agitation, 2: intense agitation. Behaviour 0: calm/sleeping,1: grimacing but can be calmed,2: frightened cannot be calmed. Verbal or bodily expression 0: calm/sleeping, 1: moderate no localised pain, 2: localised pain expressed verbally or by pointing fingers)

value; tears 0: absent, 1: present but consolable, 2: present and inconsolable; movements 0: absent, 1: moderate agitation, 2: intense agitation; behavior 0: calm/sleeping, 1: grimacing but can be calmed, 2: frightened and cannot be calmed; verbal or bodily expression 0: calm/sleeping, 1: moderate no localized pain, 2: localized pain expressed verbally or by pointing fingers. OPS score was recorded after extubation, 30 minutes, 1 hour, 6 hours, 12 hours, and 24 hours in the postoperative ward and

is shown in Figure 4. The scores were comparable between Groups C and D ($p = 0.096$; 95% CI -0.04 to 0.73) and Groups C and M ($p = 1.00$; 95% CI -0.47 to 0.3). Lower OPS scores were present in Group D compared to M ($p = 0.023$; 95% CI -0.81 to -0.04).

Watcha score was evaluated on four points (1: calm, 2: crying but consolable, 3: crying and not consolable, 4: agitated and thrashing). Scores of 1/2/3/4 were present in 33/2/0/0 (Group

C), 34/1/0/0 (Group D), and 32/2/1/0 (Group M) immediately after extubation. The scores at 30 minutes were 31/4/0/0 (Group C), 33/2/0/0 (Group D), 31/4/0/0 (Group M), while scores of 1/1/2/3/4 were present in 28/7/0/0 (Group C), 29/6/0/0 (Group D) and 24/11/0/0 (Group M) respectively at 1 hour postoperatively. The score was comparable and statistically insignificant ($p > 0.05$).

Postoperative complications observed were nausea (one patient in Group D), increased oral secretions, and tachycardia (one patient each in Groups C and M). No other postoperative complications were noted among the groups.

DISCUSSION

Our study demonstrated that preoperative oral melatonin, dexmedetomidine, and clonidine produce comparable sedation, anxiolysis, and hemodynamic stability and decrease the postoperative delirium and pain in children undergoing surgery under anesthesia.

Choice of premedicant in children should take into consideration the following factors: age of child, body weight, route of administration, physiology of pediatric age group, psychological status as per age, and underlying medical or surgical condition [12]. In the era of outpatient anesthesia, need for modification of traditional sedative premedicants is warranted. The favorable pharmacokinetics, oral preparation, adequate sedation, and anxiolytics along with decreased postoperative side effects increased the use of midazolam as an agent of choice for pediatric premedication. However, prolonged onset of action (60–90 minutes), bitter taste, and nasal irritation on transmucosal administration were few of the disadvantages of midazolam [13]. Newer drugs like clonidine, dexmedetomidine, and melatonin are emerging as effective pediatric premedicants.

α_2 agonists mediate their pharmacological effects by their action on α_{2A} , α_{2B} , and α_{2C} . α_{2A} and α_{2C} subtypes found mainly in central nervous system are responsible for sedation, analgesia, and sympatholytic. Analgesic effects are a result of stimulation of α_2 receptors in dorsal horn of spinal cord. α_{2B} receptors are usually found in vascular smooth muscles and mediate vasopressor effects [14].

Melatonin, a naturally acting hormone produced in pineal gland, produces its pharmacological effects by interacting with multiple receptor sites including opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, α adrenergic, α_2 adrenergic, and most importantly MT1/MT2 melatonergic receptors present in central nervous system as well as dorsal horn of spinal cord. Interaction of MT2 receptor and gamma aminobutyric acid (GABA) in central nervous system has been postulated as the basis of reduction in anxiety/sedation while modulation of GABA B receptors or

opioid I receptor or inhibition of NO production mediates analgesia [15].

The dosage of drugs used in our study was based on the observations from previous studies [10, 16]. Lack of suitable oral preparation of dexmedetomidine necessitated the use of intravenous preparation for oral use. This practice has been used with different intravenous agents in the past. All the drugs were administered with paracetamol syrup to increase the palatability and acceptance by children.

Pharmacokinetics of oral preparation of dexmedetomidine, clonidine, and melatonin has been studied. Oral dexmedetomidine undergoes extensive first-pass metabolism with bioavailability of 16% [17]. The drug is extensively bound to plasma protein (94%), undergoes biotransformation in liver, and has a high hepatic extraction ratio of 0.7 [18]. Hypoalbuminemia, end organ damage, change in hemodynamics, and decrease in cardiac output are responsible for high inter-individual variability in effects of dexmedetomidine. Sedation with dexmedetomidine resembles natural sleep and mimics deep recovery sleep in sleep deprivation, mediated by central pre- and postsynaptic α_2 receptors in locus coeruleus. After administration of intranasal dexmedetomidine (1–4 $\mu\text{g}/\text{kg}$) in volunteer and children significant sedation occurs with onset time of 15–45 minutes, lasting 1–2 hours [19].

Oral melatonin administration also undergoes extensive first-pass metabolism with bioavailability of 15% [20]. In their study, Andersen et al [21] have demonstrated the t_{max} of 41 minutes and concluded that values between 30 and 60 minutes are acceptable and administration 45 minutes before intended is acceptable. Age, caffeine, smoking, oral contraceptives, feeding status, critically ill patients affect pharmacokinetics [22].

Clonidine is rapidly absorbed after oral administration, and reaches peak plasma concentration within 60–90 minutes. The bioavailability of the drug is about 75–95%, with 20–40% bound to protein [23].

Sedation and separation of children from parents and ease of anesthesia induction were comparable in our study. The effects of clonidine vs dexmedetomidine and clonidine vs melatonin were similar; however, dexmedetomidine was superior to melatonin. Our study was in contrast to the study of Kumari S et al who showed midazolam to be better than clonidine and dexmedetomidine for pediatric premedication [24]. A previous study conducted by Arora S et al also reported comparable sedative effects with dexmedetomidine and clonidine in children [10]. Melatonin, used as dosage in our study, has been reported as an effective premedicant in alleviating preoperative anxiety in children.

In this study it was observed that dexmedetomidine was superior to other drugs for attenuation of the hemodynamic response to laryngoscopy and intubation, which is consistent with a previous study [25].

Objective Pain Scale was used to assess the analgesic effects of the three premedicants used in our study. Dexmedetomidine was superior to both clonidine and melatonin in influencing postoperative pain. The difference between the analgesic effects of α_2 agonists and melatonin can be attributed to the more direct analgesic effects of α_2 agonists, in addition to its anxiolytic properties, while melatonin was mainly a sedative and anxiolytic drug, dealing with the emotional component of pain rather than its sensory components [26]. Also, at doses of melatonin used in our study, it may be that the analgesic action of the drug could not be appreciated. In the randomized study conducted by Caumo et al, it was observed that oral melatonin in dose of 5 mg administered at night and 1 hour before surgery produced the adequate analgesic effect [27]. The incidence of emergence delirium was evaluated among the groups by utilizing the Watcha score. Among several pharmacological agents tried for the prevention of EA, α_2 agonists have shown promising results. α_2 agonists produce their effect by their action on the *locus ceruleus* and facilitate the release of inhibitory neurons, such as gamma aminobutyric acid system, whereas melatonin exerts its effect by activation of MT1 and MT2 receptors and modulation of GABA receptors via G-coupled protein pathway and marked dose-dependent increases in GABA concentrations in the central nervous system [28]. In a study conducted by Schmidt et al, it was found that α_2 agonists have lower incidences of postoperative anxiety and agitation [29]. Samarkandi et al, in their study, have stated melatonin as an effective premedicant in lowering the incidences of excitement and sleep disturbances postoperatively. It has been observed in previous studies that incidence of emergence delirium after premedication with 0.2 mg/kg and 0.4 mg/kg melatonin was only 8.3% and 5.4%, respectively [11]. Melatonin has a dose-dependent effect on emergence delirium. Postoperative complications were minimal and comparable.

Our study had certain limitations: first was the absence of a placebo-controlled group and, second, the drug formulation was different and the sample size was small. Age may have some influence on pharmacokinetics and pharmacodynamics of drugs. We cannot exclude the possibility that larger doses of drugs would have reduced preoperative anxiety to a greater extent than that observed here. A further study is needed to look into these aspects of observations.

CONCLUSION

Newer sedative premedicants like melatonin, clonidine, and dexmedetomidine are efficacious in producing preoperative sedation, reducing preoperative distressing anxiety, relieving postoperative pain, and decreasing the occurrence of emergence delirium in pediatric patients undergoing surgery.

These agents can be safely used as an alternative to midazolam for premedication in children.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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