ISSN 2515-8260 Volume 09, Issue 06, 2022

COMPARISON OF NEBULIZED DEXMEDETOMIDINE VERSUS COMBINATION OF NEBULIZED KETAMINE AND MIDAZOLAM FOR PREMEDICATION IN PEDIATRIC PATIENTS UNDERGOING ELECTIVE SURGERY-A RANDOMIZED DOUBLE BLINDED STUDY

1. Archana Endigeri MBBS MD., Associate Professor, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

2. Mahindra Kalashetty. MBBS MD., Associate Professor, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India.

3. Ranganath Channappagoudar MBBS MD., Assistant Professor, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India,

4.Ganeshnavar Anilkumar. MBBS MD., Professor, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India (Corresponding Author)

5. Subhash Reddy. MBBS (MD)., Junior Resident, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

6. Kelageri Satish., Junior Resident, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

7. Vidya B C. MBBS (MD)., Junior Resident, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

8. Shweta Lamani. MBBS (MD)., Junior Resident, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

Corresponding Author:

Ganeshnavar Anilkumar. MBBS MD., Professor, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

Abstract

Background & Aims: We compared dexmedetomidine with combination of midazolam and ketamine via nebulization for sedation in pediatric patients posted for elective surgery

Methods: Ethical clearance followed by informed consent was taken from guardians. Sixty was our sample size which was divided into two groups of 30 per group. Group A received dexmedetomidine 2µg/kg & Group B received midazolam 0.1 mg/kg with ketamine 1 mg/kg. The primary objective was mask acceptance scale. Secondary objectives were sedation score, parental separation anxiety scale, post operative emergence agitation, recovery times and side effects. The MS EXCEL was used for data entry & outcomes averaged as Mean with

ISSN 2515-8260 Volume 09, Issue 06, 2022

standard deviation (SD) or Median with inter quartile range (IQR). Chi-square test/ Fisher Exact test, Independent t-test/Mann-Whitney U test was used. $P < 0.05$ was regarded as remarkable.

Results: The data of demographic characteristics were non-significant in both the groups. Acceptance of mask was greater in Group B children (1.9±0.9) compared to Group A (2.8±0.97) *P*= 0.0003. Sedation was improved in Group B children (3.4±1.24) when compared to Group A (2.41±1.18). *P*= 0.04. Anxiety scale due to separation from parents, agitation at emergence, and side effects were alike. Recovery period proved shorter with Group B (83.5± 9.01 min) than Group A (105.16±6.75 min) with *P* value 0.0001.

Conclusion: combination of midazolam with ketamine provided better mask acceptance with adequate sedation and faster recovery with no significant side complications than nebulized dexmedetomidine.

Key Words: Dexmedetomidine, Ketamine, Midazolam, Nebulization, Premedication

Main points

1. Premedication is necessary for parenteral separation anxiety and reduction of post operative behavioural changes.
2. Nebulization as a newer method of premedication maximises the area of distribution, thereby causing greater absorption via airway mucosal surface, better acceptability by patients and accentuates the clinical effectiveness thereby reducing postoperative emrgence delirium.
3. Nebulized combination of low dose midazolam & ketamine provides satisfactory sedation and rapid recovery

Introduction

Period just before surgery is most distressing to pediatric patients posted for surgery. separation from parents increases their anxiety and predisposes them to post operative behavioral changes.[1] It also causes sympathetic stimulation leading to haemodynamic instability.[2] Anesthesiologists need to minimize this distress in operating room. To alleviate this anxiety various drugs have been utilized.

Midazolam is a $GABA_A$ agonist with amnestic properties and anticonvulsant actions. Ketamine is a N-methyl –d-aspartate (NMDA) opponent which provides sedation, anesthesia, analgesia and amnesia.[3] the protective reflexes are maintained.

Dexmedetomidine is a selective alpha 2 adrenergic agonist.[4] is safer and effective in children.[5]

Nebulization is easy to set up, and has got higher bioavailability. Use of nebulizer maximises the area of distribution through a spray thereby causing greater absorption via airway mucosal surface, thus achieving greater concentrations in CSF, better acceptability by patients and accentuates the clinical effectiveness.[6]

ISSN 2515-8260 Volume 09, Issue 06, 2022

Reports on drug pharmacokinetics of nebulization are few and hence we selected the dosages of ketamine,dexmeditomedine & midazolam on the basis of previous clinical studies.

The primary objective was mask acceptance on shifting into the operation theatre. Secondary objectives were sedation score, anxiety due to parental separation scale, post operative emergence agitation, recovery times & side effects if any.

Outcomes associated with sedative regimen comprising of midazolam and ketamine combination against a well proved dexmeditomedine are underreported .In literature, only few articles have used dexmeditomedine via nebulization route in children.

Intention of this research was to examine the efficacy related to nebulized dexmeditomedine in comparison to combined nebulization of midazolam and ketamine.

We hypothesised that nebulization with midazolam and ketamine premedication would be superior to dexmeditomedine in providing paediatric patients in calm phase with adequate sedation.

Materials and methods

After obtaining approval from hospital ethical committee (IECHSR/2018-19/A-79/1.1& 20/02/2019), informed consent obtained of parents or authorized guardians. Our study got registered in Clinical Trials Registry-India (CTRI/2019/03/018344). Duration of the study was from March 2019 to March 2020 with 1year period.
Sixty pediatric patients of age group 3-7 years old belonging to ASA(American Society of Anesthesiologist) physical status II, posted to undergo nonemergent surgery undergoing pediatric, orthopedic, ophthalmic and plastic surgeries under general anesthesia lasting for 30-120 minutes were involved in the study. Children presenting with upper respiratory tract infection, chronic illness, prematurity, organ dysfunction and known allergy to study drug were not included in the study.

Participants of the study were categorized into 2 groups using computer generated randomization tables obtained with computers. The anaesthetist non included in our research team revealed the group allotted by opening the opaque envelopes. opened the envelopes one hour prior to beginning the anesthesia & drugs were prepared within lookalike dispovans. Group A received Nebulized dexmedetomidine (2µg per kg) & Group B received Nebulized midazolam (0.1 mg per kg) with ketamine (1 mg per kg). The study is randomized double blinded as both patients and observer were blinded.
Drugs to be studied were dissolved in 5 ml of normal saline and administered through routine nebulizer through mouth piece with oxygen at 6 liter/min, 30 min before the surgery as the onset of sedation occurs in10-33min. Nebulization was stopped when the drug starts to sputter.

All the data observed during the study was done by an independent observer. The pulse rate (PR), blood pressure (BP), saturation of oxygen (SPO_2) & electrocardiography (ECG) were assessed at baseline & at 5min intervals.

ISSN 2515-8260 Volume 09, Issue 06, 2022

Patient's acceptance of anesthesia mask was observed utilizing 4 point mask acceptance scale[7] (MAS) which is Excellent, unafraid, co-operative, mask accepted -1; Good, slight fear of mask assured-2; Fair, moderate fear of mask not reassured-3; Poor, terrified, crying -4. MAS' scores of 1 and 2 means well accepted whereas scores of 3 and 4 means not accepted.

Sedation level was observed utilizing 5-point sedation score[7] 1=agitated, 2=alert, 3=calm, 4=drowsy, and 5=asleep. As>3 attained, the child was transferred to operation theatre. The child was observed for a time interval of 30mins for satisfactory sedation, if not sedated, child was excluded from the study.

Thirty min after sedation, anxiety due to separating from parents was observed using 4-point parental separation anxiety scale (PSAS) [7] , as Easily separated-1; Whimpers but assured -2; Cries and cannot be assured, sticking to parents-3; Cries and sticks to parents-4. PSAS of 1 and 2 signifies easy separation, scores of 3 and 4 were signifies difficult separation.

Then patient was then shifted to operation theatre. Standard monitoring like PR, NIBP, SPO2 and ECG was done every five min.

The anesthesia technique was standardized. General anaesthesia was induced with propofol 1 mg per kg, atracurium 0.5 mg per kg with 100% oxygen via Jackson Rees breathing circuit. I-gel of appropriate size was inserted and fixed after checking for bilateral equal air entry. Maintenance was done using sevoflurane 2% with 50% O_2/air . IV ketorolac 0.5mg/kg was given as intra operative analgesia followed by bolus injections of 1.0mg/kg every 6 hrs for postoperative analgesia. At the end of procedure, I-gel was taken out after thorough suctioning. The anesthesiologist who provided anesthesia was not involved in the study.

Once the airway was maintained spontaneously with hemodynamic stability, child was shifted to post anesthesia care unit (PACU). HR, BP & SPO2 were recorded at 0min, 5min, 30min, 45min and 60min. Duration of surgery was noted. Recovery was observed and time for the same was noted. Recovery time was taken with termination of anesthesia till baseline sedation. Recovery assessed using 3 point emergence agitation[8] (EA) scale which is Calm-1; Restless but calms down-2; Combative and not oriented-3. A value ≥2 suggests EA. Once the modified Aldrette recovery score [9] was >9, children were shifted from PACU.

Side effects like hypotension, bradycardia, nausea, vomiting, increased salivation and nystagmus were noted. Hypotension was considered when BP was < 20% of baseline, treated with fluids and 3mg mephentermine. Bradycardia was considered when HR< 60 beats per min, treated with injection atropine 0.02mg/kg.

Sample size calculation done utilising Open Epi Software Version 2.3.1. At 95% confidence level, 90% power of study. As per the research conducted by Abdel Ghaffar HS *et al.*,[10] the proportion of excellent mask acceptance scale (MAS) in dexmedetomidine group was 51% and in ketamine+midazolam group was 97%. The anticipated difference in the MAS for calculating sample size was 46%. As per the study we choose MAS for calculating sample size, that got to be 19 per group. To allow possible dropouts and exclusion from the study, we recruited 60 patients as shown in consort chart [Figure 1].

ISSN 2515-8260 Volume 09, Issue 06, 2022

Statistical analysis

Statistical analysis was performed using SPSS (Statistical package for social sciences) software. Owned by IBM, Chicago, IL

MS EXCEL was used for data entry and outcomes were averaged as Mean ± standard deviation (SD) or Median with inter quartile range (IQR). Chi‑square test/ Fisher Exact test, Independent t‑test/Mann‑Whitney U test The were used. $P < 0.05$ was taken as statistically significant. Kolmogorov‑Smirnov normality test was applied for all the parameters.

Results

Both the groups were similar with regards to demographic profile such as age, gender, weight, ASA physical status, and duration of surgery [Table 1].

In Group B more children (73.4%) had better mask acceptance with score of 1 and 2 than in Group A (30%), P=0.05 [Figure 2].

Sedation after 30 min was significantly better in Group B compared to Group A. Maximum children with score of 4 and 5 was (50%) in Group B, and (16.70%) in Group A. $P = 0.04$ [Figure 3].

Other variables like parental separation anxiety, emergence agitation were almost similar in both the groups [Table 2].

The recovery times were significantly less in Group B compared to Group A. Basal PR, mean arterial pressure (MAP) and SPO_2 were comparable.

Complication like increased salivation was observed in 2 patients in Group B. 2 patients in Group A developed significant bradyacardia & hypotension postoperatively.

Discussion

Pediatric premedication is a challenging situation. Several drugs have been tried by various routes for preanesthetic sedation. We studied a group of children who were posted for various surgeries under general anesthesia. We chose general anesthesia because it was possible to use a stadardized anesthetic technique with minimum confounding factors.

Our results of sedation score are similar to H.S.Abdel-Ghaffar. *et al*.,[10] they got higher mask acceptance in group D (P<0.015), this is not similar to our study as we got better mask acceptance in group B. In their study, children in Group D showed higher sedation (P<0.03); and better parental separation anxiety scale (P<0.044).We did not get similar result; it could be because we compared dexmeditomedine against a synergistic combination of midazolam and ketamine. Recovery time was significantly less in Group D (5.5 min) compared to Group K (10 min) and M (8 min) in their study, this is not similar to our study.

The significant differences recorded between the studies suggests the different type of sedation. Sedation of dexmedetomidine is represented as arousable sedate state unlike other

sedatives.[11,12]. Another reason could be that Gaffer *et al*., used individual drugs in 3 groups whereas we used combined midazolam and ketamine against dexmedetomidine.

BABITA GHAI. *et al*.,[13] found that combined midazolam & ketamine effectively relieves from anxiety & parental separation features.We got similar results in our study.

Ji-Feng Feng. *et al*.,[14] compared dexmedetomidine against midazolam for premedication in children.They concluded that patients in dexmedetomidine group got significantly satisfactory sedation (RR=0.71) and parental separation (RR=0.56) than patients in the midazolam group. However these results were not similar in our study because we utilised midazolam and ketamine combination.

KAJAL JAIN. *et al*.,[15] found that when midazolam and ketamine was compared against midazolam Group MK provided more patients in clam state in comparison to group M (*P*=0.02). The results are similar to our study. They proved that midazolam and ketamine would enhance effects of premedication than the drugs used alone.

The limitation of our research is sedation score we used system to determine the sedation characteristics. Although same score is used in various researches , it has not been formally established and the intra and inter variability is yet to be proved. Our sample is low; a larger sample is required to determine the impact of premedication on pivotal postoperative outcome such as anxiety. Also, there is lack of follow up for the delayed side effects, upto 48h.

Nebulized route is underutilized in children and MORE drug combinations and dose finding studies are required. Premedication in children with previous negative experiences, impacting subsequent behaviour changes, should be studied. Our study outcomes can be utilised for metaanalysis or systemic reviews.

Conclusion

Nebulized combination of low dose midazolam & ketamine produced satisfactory mask acceptance adequate sedation with rapid recovery with no significant side effects than nebulized dexmedetomidine.

BIBLIOGRAPHY

1) Kain, Z. N., Caldwell-Andrews, A. A., Krivutza, D. M., Weinberg, M. E., Wang, S. M., & Gaal, D. (2004). Trends in the practice of parental presence during induction of anesthesia and the use of preoperative sedative premedication in the United States, 1995–2002: results of a follow-up national survey. *Anesthesia & Analgesia*, *98*(5), 1252-1259.

2) Davidson, A., & McKenzie, I. (2011). Distress at induction: prevention and consequences. *Current Opinion in Anesthesiology*, *24*(3), 301-306.

3) Khatavkar, S. S., & Bakhshi, R. G. (2014). Comparison of nasal midazolam with ketamine versus nasal midazolam as a premedication in children. *Saudi journal of anaesthesia*, *8*(1), 17.

4) Schmidt, A. P., Valinetti, E. A., Bandeira, D., Bertacchi, M. F., Simoes, C. M., & Auler Jr, J. O. C. (2007). Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. *Pediatric Anesthesia*, *17*(7), 667-674.

5) Uusalo, P., Guillaume, S., Siren, S., Manner, T., Vilo, S., Scheinin, M., & Saari, T. I. (2020). Pharmacokinetics and sedative effects of intranasal dexmedetomidine in ambulatory pediatric patients. *Anesthesia & Analgesia*, *130*(4), 949-957.

6) Zanaty, O. M., & El Metainy, S. A. (2015). A comparative evaluation of nebulized dexmedetomidine, nebulized ketamine, and their combination as premedication for outpatient pediatric dental surgery. *Anesthesia & Analgesia*, *121*(1), 167-171.

7) Wilton, N. C., Leigh, J., Rosen, D. R., & Pandit, U. A. (1988). Preanesthetic sedation of preschool children using intranasal midazolam. *The Journal of the American Society of Anesthesiologists*, *69*(6), 972-974.

8) Bajwa, S. A., Costi, D., & Cyna, A. M. (2010). A comparison of emergence delirium scales following general anesthesia in children. *Pediatric Anesthesia*, *20*(8), 704-711.

9) Jain, A., Muralidhar, V., Aneja, S., & Sharma, A. K. (2018). A prospective observational study comparing criteria-based discharge method with traditional time-based discharge method for discharging patients from post-anaesthesia care unit undergoing ambulatory or outpatient minor surgeries under general anaesthesia. *Indian journal of anaesthesia*, *62*(1), 61.

10) Abdel-Ghaffar, H. S., Kamal, S. M., El Sherif, F. A., & Mohamed, S. A. (2018). Comparison of nebulised dexmedetomidine, ketamine, or midazolam for premedication in preschool children undergoing bone marrow biopsy. *British Journal of Anaesthesia*, *121*(2), 445-452.

11) McCormick, A. S. M., Thomas, V. L., Berry, D., & Thomas, P. W. (2008). Plasma concentrations and sedation scores after nebulized and intranasal midazolam in healthy volunteers. *British journal of anaesthesia*, *100*(5), 631-636.

12) Nelson, L. E., Lu, J., Guo, T., Saper, C. B., Franks, N. P., & Maze, M. (2003). The α2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *The Journal of the American Society of Anesthesiologists*, *98*(2), 428-436.

13) Ghai, B., Grandhe, R. P., Kumar, A., & Chari, P. (2005). Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication. *Pediatric anesthesia*, *15*(7), 554-559.

14) Feng, J. F., Wang, X. X., Lu, Y. Y., Pang, D. G., Peng, W., & Mo, J. L. (2017). Effects of dexmedetomidine versus midazolam for premedication in paediatric anaesthesia with sevoflurane: A meta-analysis. *Journal of International Medical Research*, *45*(3), 912-923.

15) Jain, K., Ghai, B., Saxena, A. K., Saini, D., & Khandelwal, N. (2010). Efficacy of two oral premedicants: midazolam or a low-dose combination of midazolam–ketamine for reducing stress during intravenous cannulation in children undergoing CT imaging. *Pediatric anesthesia*, *20*(4), 330-337.

Legends

Figure 1: Consort chart
Figure 2: Mask acceptance scale
Figure 3: Degree of sedation
Table 1: Demographic characteristics of patients
Table 2: Characteristics of Patient acceptance of medication, Parental separation anxiety, and Emergence Agitation and Recovery times.

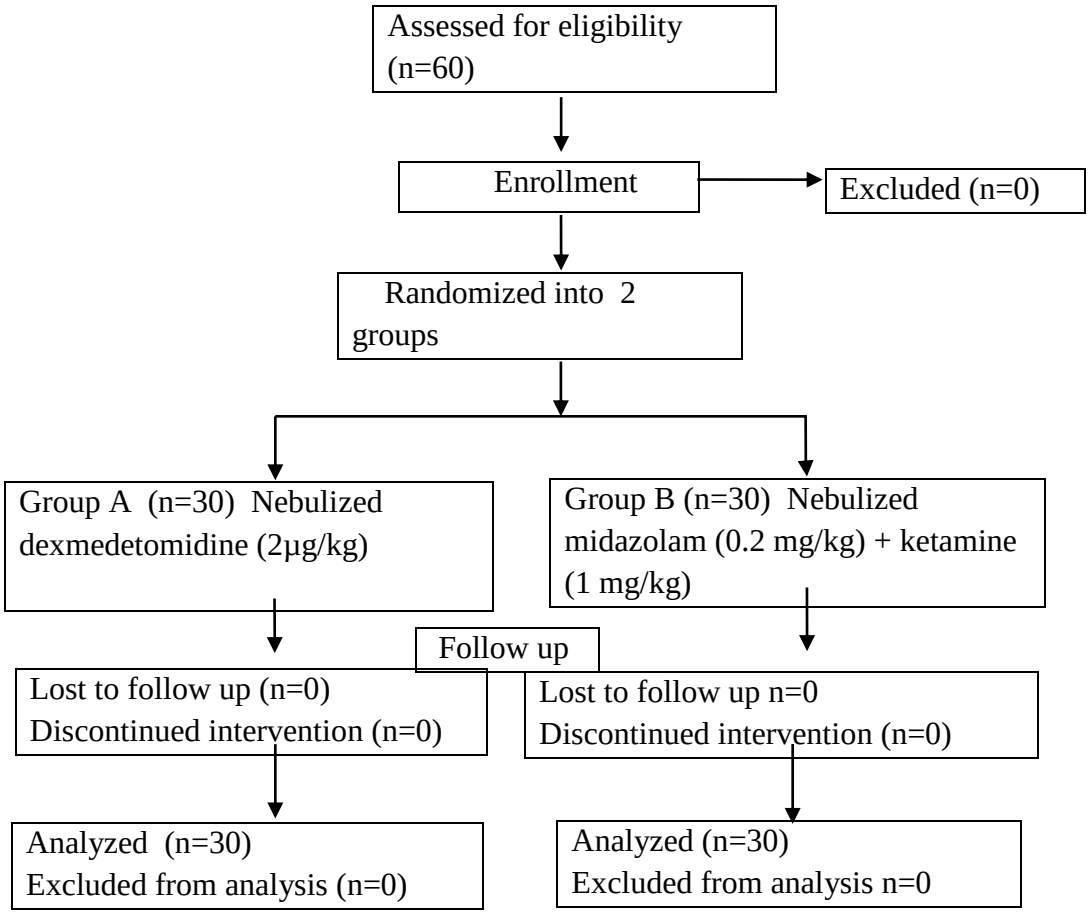
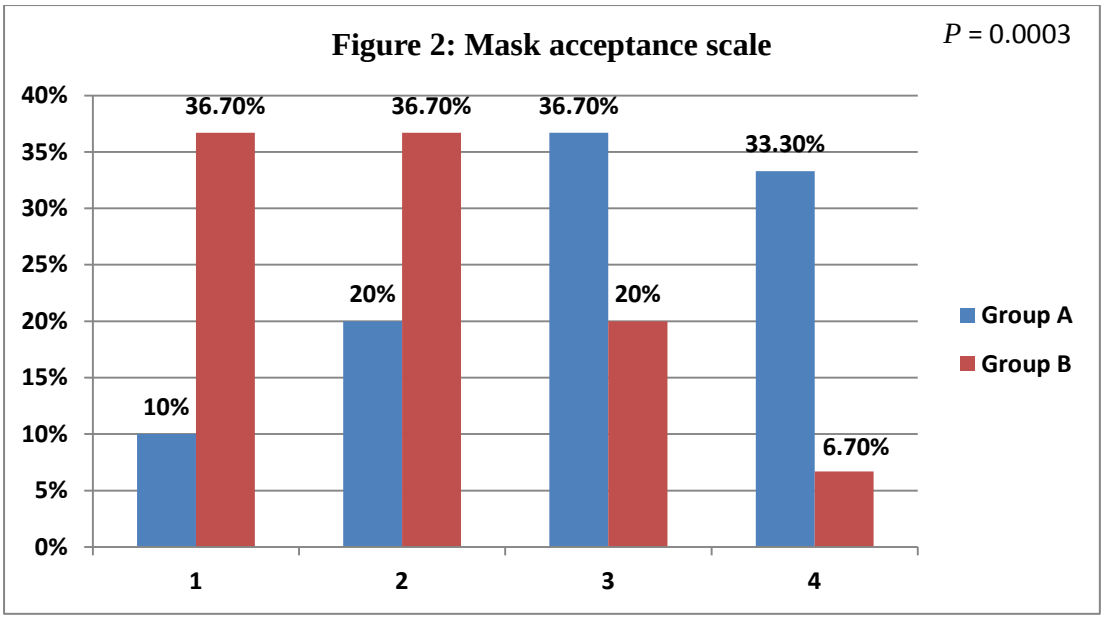
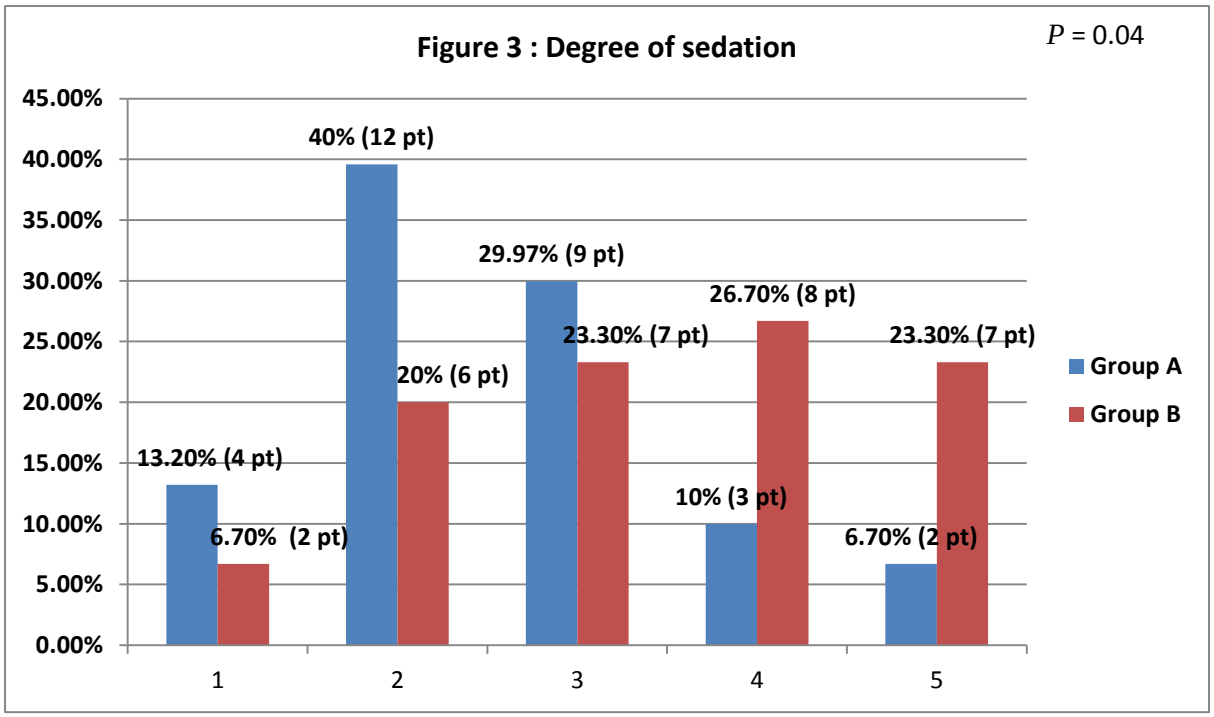


Figure 1: Consort chart

ISSN 2515-8260 Volume 09, Issue 06, 2022





Demographic Data	Group A (n=30)	Group B (n=30)	*P* value
Age in years (mean±SD)	4.57± 1.41	4.47± 1.36	0.780

Weight in kgs (mean±SD)	13.00± 5.29	12.67± 5.12	0.805
Gender (Male:Female)	25:5	23:7	
ASA (I/II/III)	15/10/5	16/12/2	
Duration of surgery in minutes (mean±SD)	63.5±16.55	62.16±11.79	0.7188

*ASA – American Society of Anesthesiologists, *MPC- Mallampati Classification *SD-standard deviation, *P<0.05.

Table 1: Demographic characteristics of patients

Variable	Group A	Group B	*P*-value
Patient acceptance of medication (mean±SD)	2.345± 0.9364	2.233±0.8976	0.66
Parental separation anxiety (mean±SD)	2.276± 0.9218	2.1± 0.9229	0.59
Emergence Agitation (mean±SD)	2.034± 0.7784	1.767± 0.7279	0.17
Recoverytimes in minutes (mean±SD)	105.16±6.75	83.5± 9.016269	<0.0001

*SD-standard deviation, *P<0.05.

Table 2: Characteristics of Patient acceptance of medication, Parental separation anxiety, and Emergence Agitation and Recovery times.

ISSN 2515-8260 Volume 09, Issue 06, 2022

Author details

1. Archana Endigeri MBBS MD., Associate Professor, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

2. Mahindra Kalashetty. MBBS MD., Associate Professor, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India.

3. Ranganath Channappagoudar MBBS MD., Assistant Professor, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India,

4.Ganeshnavar Anilkumar. MBBS MD., Professor, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India **(Corresponding Author)**

5. Subhash Reddy. MBBS (MD)., Junior Resident, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

6. Kelageri Satish., Junior Resident, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

7. Vidya B C. MBBS (MD)., Junior Resident, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

8. Shweta Lamani. MBBS (MD)., Junior Resident, Department Of Anaesthesiology, S N Medical College & HSK Hospital, Bagalkot, Karnataka, India

ISSN 2515-8260 Volume 09, Issue 06, 2022

Receipt

Field	Value
PG Order ID	218509148
Transaction ID	RPUPIU17176282378
Payment Date	2022-07-30 10:25:08
Payment Status	Paid
Name	Anilkumar Ganeshnavar
Phone	9964526598
Email	anilganesh22@gmail.com
Amount Paid	₹ 6000.00
Purpose of Payment	Open access charges of the article

Manuscript title “Comparison of Nebulized Dexmedetomidine Versus Combination Of Nebulized Ketamine And Midazolam For Premedication In Pediatric patients Undergoing Elective Surgery-A Randomized Double Blinded Study”