

Comparative Study of Oral Dexmedetomidine Versus Oral Midazolam As Premedication In Paediatric Elective Surgeries

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ABSTRACT

BACKGROUND

Almost 50% of children undergoing surgery shows signs of significant preoperative anxiety and fear and may not be cooperative to anaesthesia. Untreated anxiety may lead to difficult induction, greater need of rescue analgesia and post operative psychological effects and behavioral issues. Psychological trauma and distress for both children and parents are major challenges in paediatric anaesthesia. Hence premedication is used not only to produce amnesia but to allay fear and anxiety and to provide calm and cooperative child for smooth induction. We preferred oral form of premedication drugs to which children will be more complaint.

AIM : To compare the efficacy of oral Dexmedetomidine versus oral Midazolam in paediatric elective surgeries in terms of acceptance of premedication, effective sedation, anxiolysis, parental separation anxiety, mask acceptance behavior.

METHODS : 100 children of age group 2 to 12 years weighing less than 20 kgs of ASA I and II undergoing elective paediatric surgeries were randomized into two groups, group M received oral Midazolam 0.5 mg/ kg (preservative free drug containing 5 mg/ml). Group D received oral Dexmedetomidine 2 µg/ kg (preservative free drug containing 100 µg/ ml). Both the drug administered with 5% dextrose with volume adjusted to 5ml, 45 minutes prior to induction of anaesthesia. Following parameters were measured in terms of acceptance of premedication, effective sedation, anxiolysis, parental separation anxiety, mask acceptance behaviour were recorded and statistically analysed using SPSS version 20. Haemodynamic parameters were assessed and compared pre operative, intra operative and post operatively.

RESULT : Midazolam showed better result in reducing anxiety, easy parental separation, and excellent mask acceptance. Whereas in terms of acceptance of premedication, sedation and haemodynamic stability both midazolam and Dexmedetomidine produced equal effects.

CONCLUSION: We conclude that oral Midazolam is a superior and safe pre-medicant in paediatric patients had faster onset of sedation, provided satisfactory sedation, lower anxiety score, easy parental separation and excellent mask acceptance as compared to Dexmedetomidine.

KEYWORD: Midazolam, Dexmedetomidine, Pre-medication.

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I. Introduction

Most of the children posted for surgery shows sign of significant preoperative anxiety with fear and may be uncooperative to surgeries and anaesthesia. Untreated anxiety may lead to difficulty in induction, increased postoperative pain and stress, need of rescue analgesics, emergence delirium and postoperative psychological effects and behavioural issues.

Distress and psychological trauma for both children and parents are major challenges in paediatric anaesthesia². The anticipation of pain, separation from family and fear of surgery are few factors that trigger preoperative anxiety.

Hence premedication is required for reducing anxiety in children, struggling against mask acceptance during induction of anaesthesia and proper premedication provide calm and cooperative child for smooth induction.

PRIMARY OBJECTIVE :

To compare the efficacy of oral Dexmedetomidine versus oral Midazolam in paediatric elective surgeries in terms of acceptance of premedication, effective sedation, anxiolysis, parental separation anxiety, mask acceptance behaviour.

SECONDARY OBJECTIVE

Comparison of haemodynamic responses between oral Dexmedetomidine and oral Midazolam preoperative, intra operative and post operative periods for two hours

II. Materials And Methodology

STUDY DESIGN

This is a prospective double blinded randomized controlled clinical trial. Since it is time bound study all cases who met inclusion criteria during the study period had included. Randomization was done by draw of lots method. Midazolam and Dexmedetomidine written on equal number of lots ,50 each.

STUDY PLACE

Coimbatore medical college hospital ; paediatric surgery operation theatre.

STUDY PERIOD

Period of one year .

STUDY POPULATION

After clearance from institutional ethical committee and after obtaining informed written consent from parents this study was conducted with sample size of 100 children of both sexes of age 2-12 years scheduled for paediatric elective surgeries of American society of anaesthesiology of physical status **I** and **II** Sample size was calculated with G*power 3.13 version with reference to parent Study.

SELECTION CRITERIA

INCLUSION CRITERIA

- ASA **I** and **II** physical status
- 2-12 years weighing less than 20 kg
- Elective paediatric surgeries

EXCLUSION CRITERIA

- ASA physical status **III** and **IV**
- Hepatic and renal complication
- Emergency operation
- Mental disability
- History of allergy to midazolam and dexmedetomidine
- Abnormal airway
- Active respiratory tract infection
- Raised intracranial pressure
- Depressed conscious level

GROUPS

GROUP M ; 50 children receiving oral midazolam 0.5 mg/kg

GROUP D ; 50 children receiving oral dexmedetomidine 2ug/kg

III. Methodology

100 children with average age of 2-12 years undergoing elective paediatric surgeries under general anaesthesia were randomized into two groups of 50 each by draw of lots method. A complete pre anaesthetic evaluation was done and the parents were explained about the effects ,possible risks and complication of the premedicants in detail and informed written consent was obtained. The child was shifted to premedication room along with their parents. Baseline Haemodynamic parameters such as heart rate ,respiratory rate, blood pressure, oxygen saturation are recorded as baseline. Oral midazolam 0.5mg/kg (IV drug containing 5mg/ml made into total volume of 0.2ml/kg mixed with 5% dextrose). Oral dexmedetomidine 2ug/kg (IV containing 100ug/ml mixed with 5% dextrose into total volume of 0.2ml/kg). Amount of drug adjusted to 5ml for all. The drug was administered using drug filler according to stipulated group the child belongs to ,by the assistant professor who was not involved in the study 45 minutes prior to induction of anaesthesia. Haemodynamic paramaters were monitored every 15 minutes after Premedication, intra operatively and for postoperative periods of 2hours. The following paramaters were assessed and recorded 6 .

ACCEPTANCE OF PREMEDICATION ON THREE POINT SCALE

- **1** = Accepts it / likes the taste
- **2** = Accepts it / but dislikes the taste

- 3 = Spits / vomits the premedication
- Score 1 or 2 was considered as satisfactory acceptance of oral Premedication. On arrival in operation theatre, the children's baseline heart rate, blood pressure, respiratory rate, oxygen saturation was recorded. Following parameters was assessed and recorded using appropriate scales respectively.

DEGREE OF SEDATION ON THREE POINT SCALE

- 1 = Awake
- 2 = Drowsy
- 3 = Asleep

Score of 2 or 3 was considered as acceptable sedation.

ANXIETY SCALE ASSESSED ON A FIVE POINT SCALE

- 1 = Quiet and comfortable
- 2 = Uneasy
- 3 = Worried or anxious
- 4 = Very worried or very upset
- 5 = Frightened or terrified

Score of 1 or 2 was considered as acceptable anxiolysis.

Behavior of child on separation from parents was assessed and recorded on four point scale.

PARENT SEPARATION ANXIETY SCALE

- 1 = Easy separation
- 2 = Whimpers but is easily reassured
- 3 = Cries and cannot be easily reassured, but not clinging to parents
- 4 = Cries and clinging to parents

Score of 1 and 2 was considered as acceptable.

MASK ACCEPTANCE BEHAVIOUR ASSESSED ON FOUR POINT SCALE

- 1 = Calm and cooperating
- 2 = Anxious but without resistance
- 3 = Anxious with slight resistance
- 4 = Crying and /or struggling against mask

Score of 1 and 2 was considered as acceptable.

All children were uniformly given inj. atropine 10ug/kg and inj. fentanyl 2ug/kg IV as premedication. Adequately preoxygenated and induced with inj. propofol 2mg/kg, inj. atracurium 0.5mg/kg and intubated with appropriate sized endotracheal tubes. Maintained with O₂/ N₂O mixture at 4 litres of fresh gas flow at 50:50 ratio, and sevoflurane 0.2-0.4%. Intraoperative haemodynamic parameters monitored every 15 minutes and recorded. At the end of surgery after adequate airway reflexes and adequate muscle power by reversal with inj. neostigmine 50ug/kg and inj. atropine 10ug/kg patient extubated in lateral position. Post operatively pulse rate, blood pressure, oxygen saturation and respiratory rate was recorded every thirty minutes for two hours.

STATISTICAL ANALYSIS

Datas collected from the study were statistically analysed. The collected data was analysed with IBM SPSS 20 version. To describe about the data descriptive statistics frequency analysis used, percentage analysis were used for categorical variables and for continuous variables the mean and standard deviation were used. To find the significance difference between the bivariate samples in paired groups paired sample t-test used for the normal data and for Independent variables between the groups (Midazolam and Dexmedetomidine) unpaired sample t-test for the normal data was used. For the multivariate analysis the repeated measures of two way Anova test was used. To find the significance in categorical data Chi-square test was used. In all the above statistical tools the probability value < 0.05 is considered as significant level.

IV. Observation And Results

- P value < 0.01 Highly Significant
- P value < 0.05 Significant
- P value ≥ 0.05 Not Significant

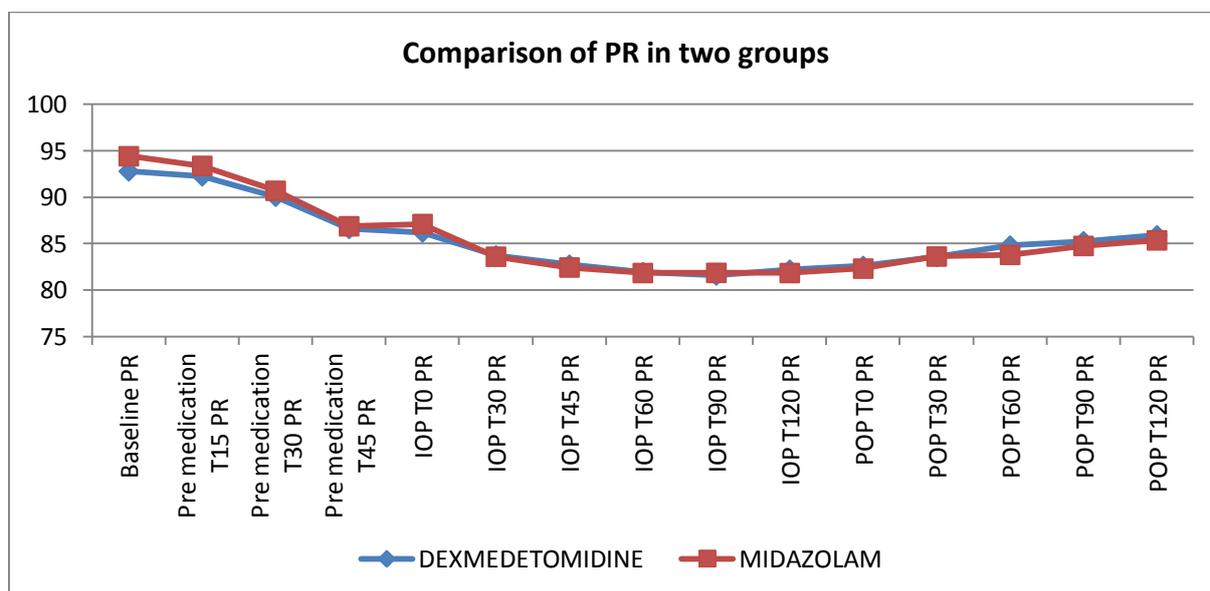
DEMOGRAPHIC VARIABLES

| Independent Samples Test | | | | | | | |
|--------------------------|-----------------|----|--------|----------------|-----------------|---------|---------|
| | GROUP | N | Mean | Std. Deviation | Std. Error Mean | t Value | P Value |
| Age | DEXMEDETOMIDINE | 50 | 3.8300 | 1.73679 | .24562 | 0.831 | 0.408 |
| | MIDAZOLAM | 50 | 4.1200 | 1.75418 | .24808 | | |

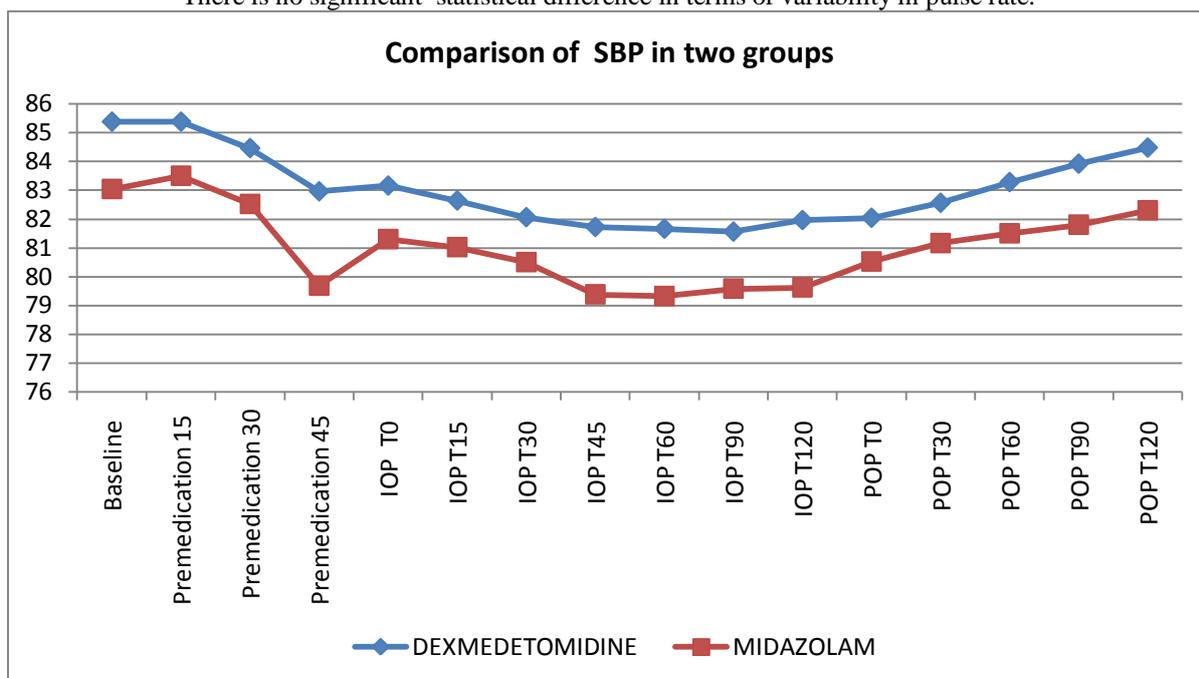
There is no statistical significant difference (p > 0.05) between two groups in terms of age.

| Independent Samples Test | | | | | | | |
|--------------------------|-----------------|----|---------|----------------|-----------------|---------|---------|
| | GROUP | N | Mean | Std. Deviation | Std. Error Mean | t Value | P Value |
| Weight | DEXMEDETOMIDINE | 50 | 11.5000 | 3.82393 | .54079 | 0.604 | 0.547 |
| | MIDAZOLAM | 50 | 12.0000 | 4.43087 | .62662 | | |

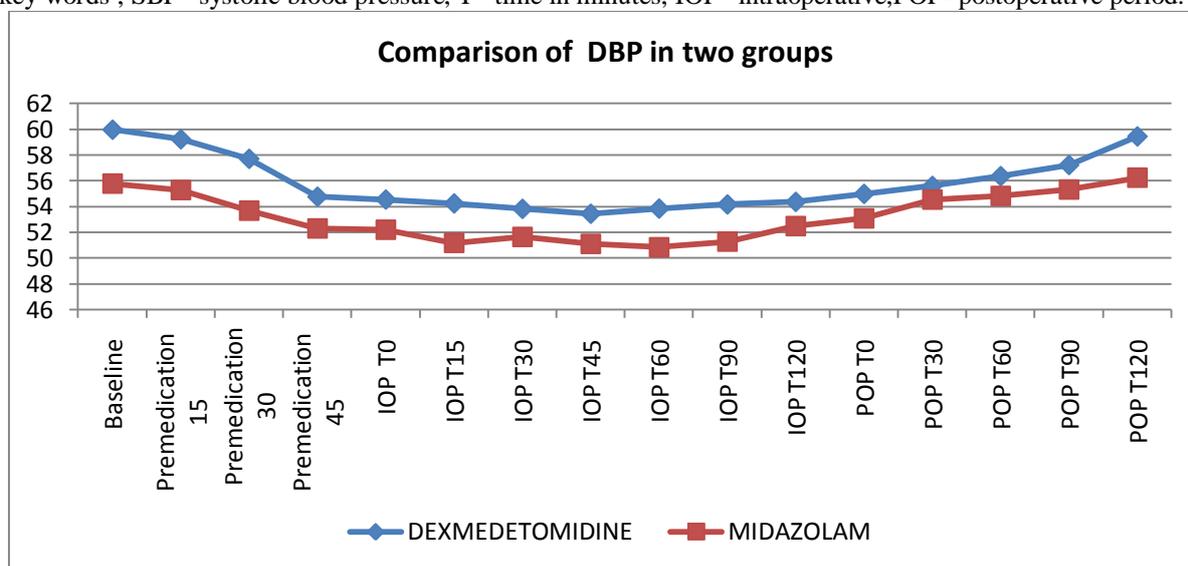
P>0.05 No statistical significant difference in Weight between the two groups.

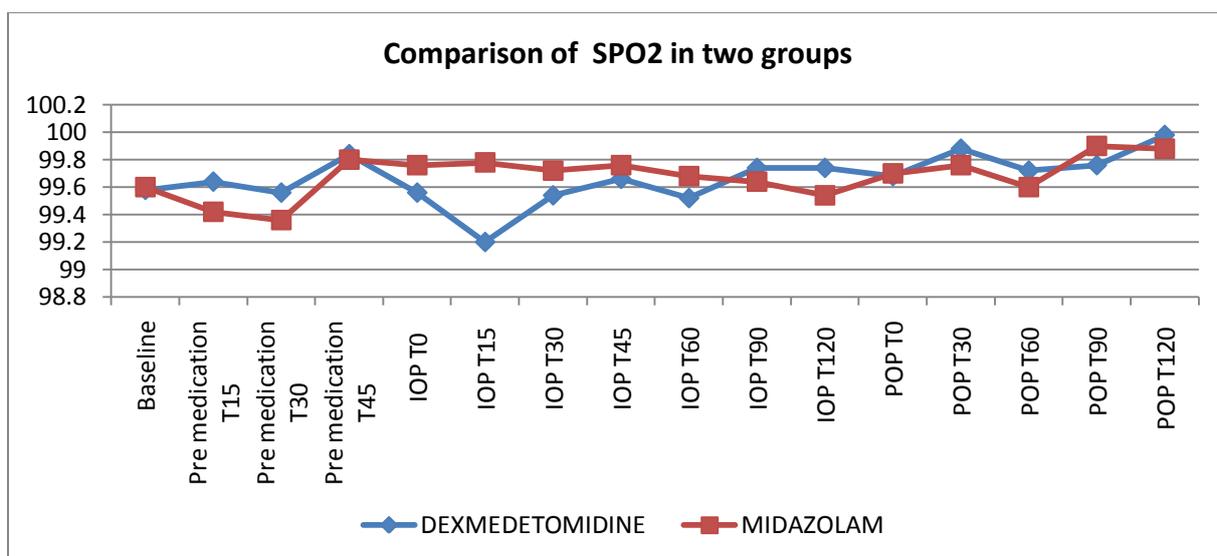
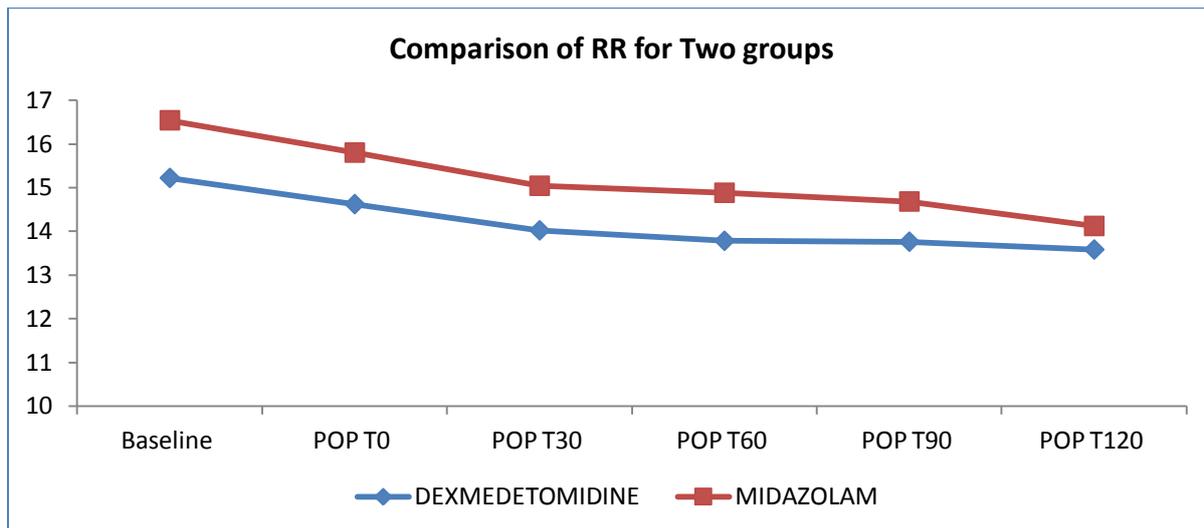


There is no significant statistical difference in terms of variability in pulse rate.



key words ; SBP –systolic blood pressure, T –time in minutes, IOP –intraoperative,POP- postoperative period.



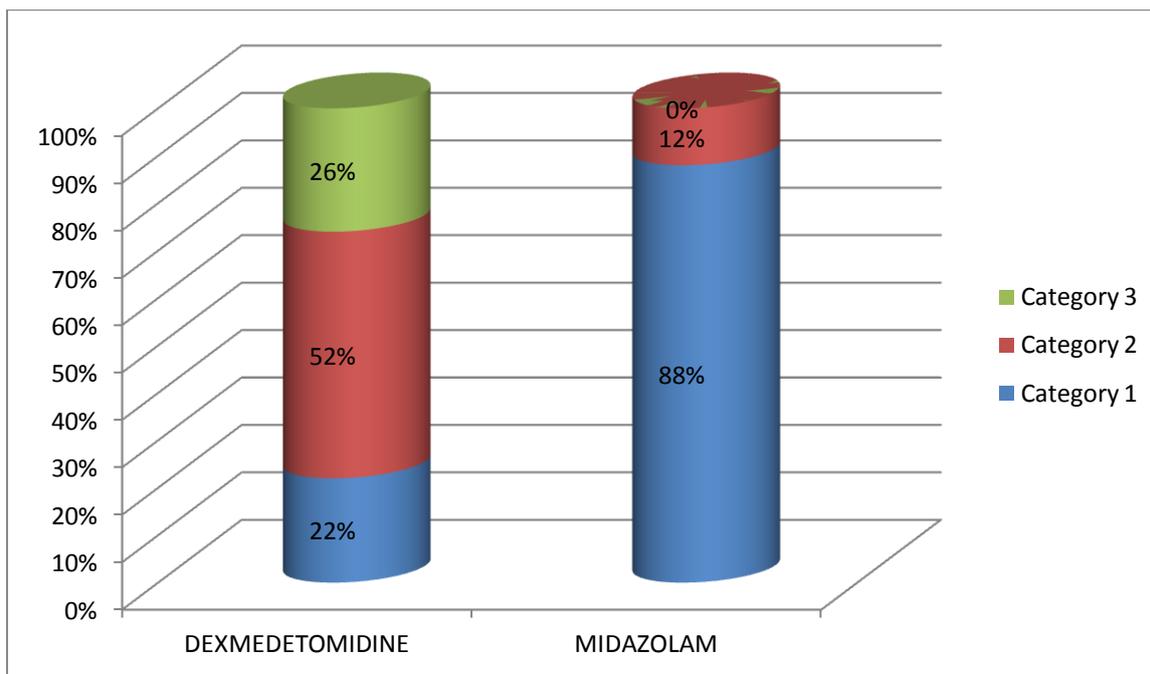


As evident from above statistical analysis , there is no significant variation of heart rate, bloodpressure ,respiratory rate and oxygen saturation between both the drug groups. However MIDAZOLAM shows better haemodynamic responses when compared to DEXMEDETOMIDINE .

ANXIETY SCALE Crosstab

| | | | GROUP | | Total |
|---------------|------|----------------|-----------------|-----------|--------|
| | | | DEXMEDETOMIDINE | MIDAZOLAM | |
| ANXIETY SCALE | 1.00 | Count | 11 | 44 | 55 |
| | | % within GROUP | 22.0% | 88.0% | 55.0% |
| | 2.00 | Count | 26 | 6 | 32 |
| | | % within GROUP | 52.0% | 12.0% | 32.0% |
| | 3.00 | Count | 13 | 0 | 13 |
| | | % within GROUP | 26.0% | 0.0% | 13.0% |
| Total | | Count | 50 | 50 | 100 |
| | | % within GROUP | 100.0% | 100.0% | 100.0% |

Pearson Chi-Square=45.30**p<0.001

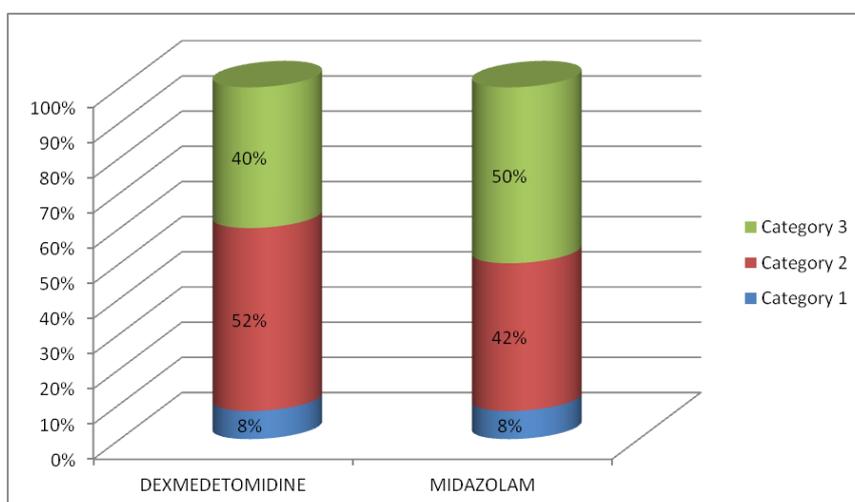


In midazolam group 44 children were quiet and comfortable, 6 children were uneasy. Whereas in dexmedetomidine only 11 children were quiet, 26 were uneasy, 13 were anxious. There is significant statistical difference between the groups in terms of anxiety ($p < 0.01$).

SEDATION SCALE Cross tabulation

| | | | GROUP | | Total |
|----------------|------|----------------|-----------------|-----------|--------|
| | | | DEXMEDETOMIDINE | MIDAZOLAM | |
| SEDATION SCALE | 1.00 | Count | 4 | 4 | 8 |
| | | % within GROUP | 8.0% | 8.0% | 8.0% |
| | 2.00 | Count | 26 | 21 | 47 |
| | | % within GROUP | 52.0% | 42.0% | 47.0% |
| | 3.00 | Count | 20 | 25 | 45 |
| | | % within GROUP | 40.0% | 50.0% | 45.0% |
| Total | | Count | 50 | 50 | 100 |
| | | % within GROUP | 100.0% | 100.0% | 100.0% |

Pearson Chi-Square=1.087 $p=0.581$

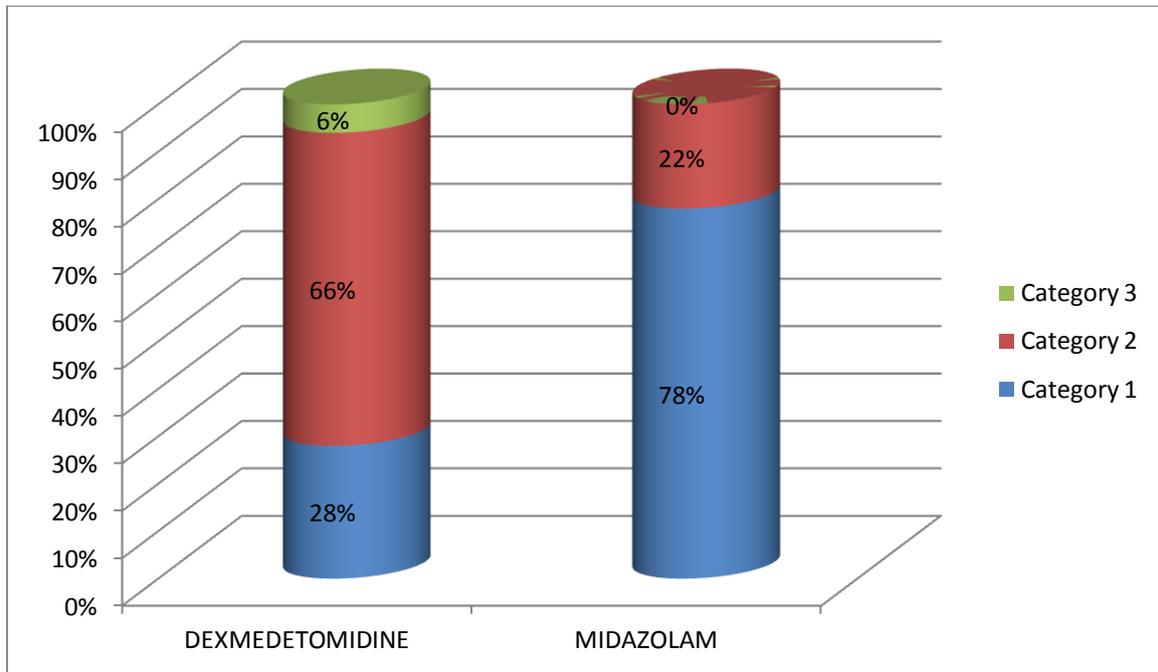


In dexmedetomidine and midazolam group 20 and 25 children were fully asleep, 26 and 21 children were drowsy, 4 children in both the group were awake respectively. There is no statistical significant difference between the groups ($p=0.581$).

PARENTAL SEPARATION ANXIETY SCALE Cross tab

| | | | GROUP | | Total |
|-------|----------------|----------------|-----------------|-----------|-------|
| | | | DEXMEDETOMIDINE | MIDAZOLAM | |
| PSAS | 1.00 | Count | 14 | 39 | 53 |
| | | % within GROUP | 28.0% | 78.0% | 53.0% |
| | 2.00 | Count | 33 | 11 | 44 |
| | | % within GROUP | 66.0% | 22.0% | 44.0% |
| | 3.00 | Count | 3 | 0 | 3 |
| | | % within GROUP | 6.0% | 0.0% | 3.0% |
| Total | Count | 50 | 50 | 100 | |
| | % within GROUP | 100.0% | 100.0% | 100.0% | |

Pearson Chi-Square=25.79**p<0.001



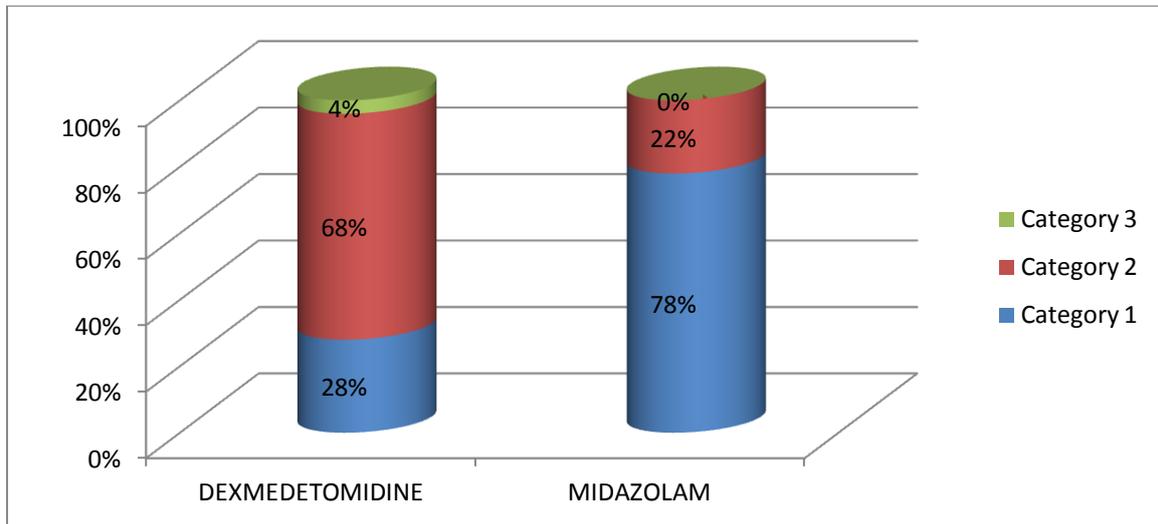
For midazolam groups 39 were easily separated from parents,11 whimpers but reassurable, whereas in dexmedetomidine only 14 were easily separable,33 whimpers but reassurable.3 cries and not reassurable. None of children of both groups were clinging to parents.

There is statistical significant difference between the groups (p<0.01).

MASK ACCEPTANCE SCALE Crosstab

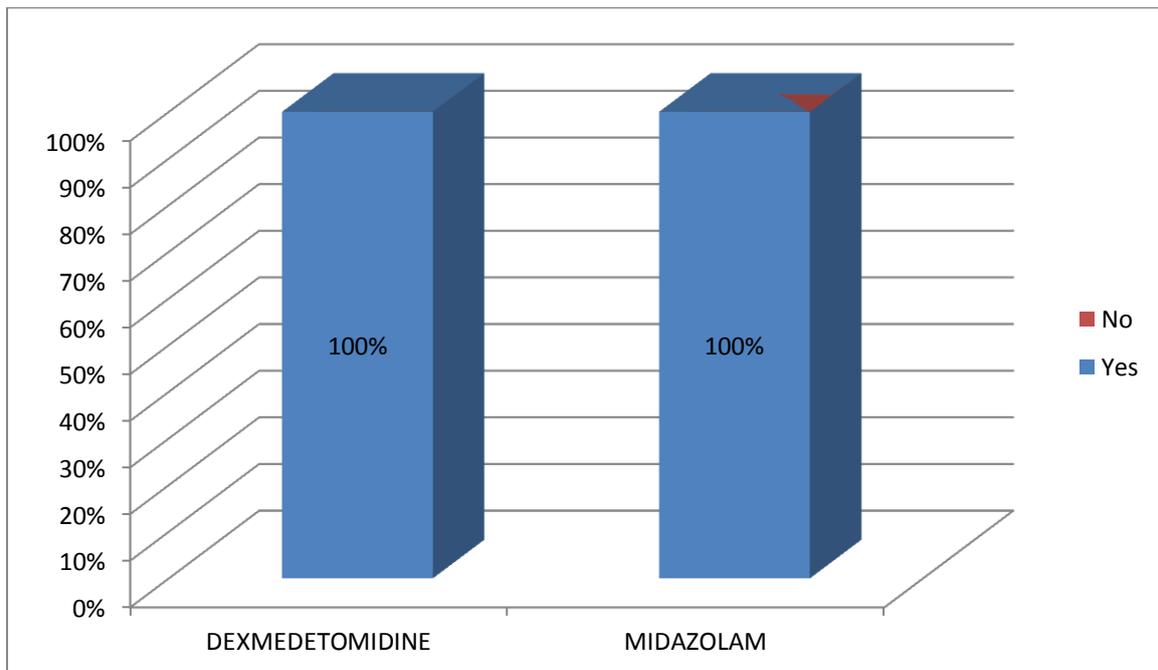
| | | | GROUP | | Total |
|-----------------|----------------|----------------|-----------------|-----------|-------|
| | | | DEXMEDETOMIDINE | MIDAZOLAM | |
| MASK ACCEPTANCE | 1.00 | Count | 14 | 39 | 53 |
| | | % within GROUP | 28.0% | 78.0% | 53.0% |
| | 2.00 | Count | 34 | 11 | 45 |
| | | % within GROUP | 68.0% | 22.0% | 45.0% |
| | 3.00 | Count | 2 | 0 | 2 |
| | | % within GROUP | 4.0% | 0.0% | 2.0% |
| Total | Count | 50 | 50 | 100 | |
| | % within GROUP | 100.0% | 100.0% | 100.0% | |

Pearson Chi-Square=25.55**p<0.001



In midazolam group of children 39 were calm and cooperative, 11 were anxious without resistance. Whereas in dexmedetomidine 14 were calm and cooperative, 34 were anxious without resistance, 2 were anxious with slight resistance. None of children were struggled against the mask. There is statistical high significant difference between the groups ($p < 0.001$).

| | | GROUP | | Total | |
|-----------------------------|-----|-----------------|-----------|--------|--------|
| | | DEXMEDETOMIDINE | MIDAZOLAM | | |
| ACCEPTANCE OF PREMEDICATION | Yes | Count | 50 | 50 | 100 |
| | | % within GROUP | 100.0% | 100.0% | 100.0% |
| Total | | Count | 50 | 50 | 100 |
| | | % within GROUP | 100.0% | 100.0% | 100.0% |



All the children accepted the premedication of both the drugs. None of them spits the drug. There is no statistical significant difference between the groups. ($p = 0.424$).

ASA physical status * GROUP Cross tabulation

| | | | GROUP | | Total |
|-------|------|----------------|-----------------|-----------|--------|
| | | | DEXMEDETOMIDINE | MIDAZOLAM | |
| ASAPS | 1.00 | Count | 43 | 40 | 83 |
| | | % within GROUP | 86.0% | 80.0% | 83.0% |
| | 2.00 | Count | 7 | 10 | 17 |
| | | % within GROUP | 14.0% | 20.0% | 17.0% |
| Total | | Count | 50 | 50 | 100 |
| | | % within GROUP | 100.0% | 100.0% | 100.0% |

Pearson Chi-Square=0.638 p=0.424

40 children of midazolam group were in physical status 1, and in spite of 10 in physical status II. In dexmedetomidine 43 children were in physical status I, only 7 in physical status II. There is no statistical significant difference between the groups. (p =0.424).

V. Discussion

Pre medication in children is mandatory to reduce fear and anxiety prior to surgery and to provide smoother induction for anaesthesia. In search of effective premedicant we had done this study to find out good premedicant and chosen to compare oral midazolam and oral dexmedetomidine as a premedicant in paediatric elective surgeries. The sample size of 98 was arrived with G *power 3.13 version with reference to previous parent study. Accounting for drop outs 100 cases were taken into study. ASA PS I and II was selected since there wont be any major side effects by the drug or any coexisting conditions. The maximum allowable weight in the study was 20kg to avoid large volume of drug as premedication. All the specified study mentioned had accepted ASA PS I AND II patients for their study 23, 27. The dose of drug of midazolam was chosen based on the parent study by Mc Millan et al 7, which concluded that oral midazolam given at a dose of 0.5mg/kg was effective at causing sedation without any side effects. Fazi et al 15, in a study to compare oral midazolam and clonidine for sedation of paediatric tonsillectomy patients used midazolam as 0.5mg/kg. Kamal k et al 17 studies have compared the oral dexmedetomidine versus oral midazolam as premedication in paediatric anaesthesia Sarika kumari et al 5 in the study comparison of oral clonidine, oral dexmedetomidine, and oral midazolam for premedication in paediatric patients used midazolam 0.5mg/kg (since 0.75 mg/kg caused more side effects 8), dexmedetomidine 4ug/kg and oral clonidine 4 ug/kg. In this study after oral dexmedetomidine 2ug/kg maximum serum concentration achieved in 2.2± 0.5 hr. The plasma concentration of dexmedetomidine that produce sedation in children is 0.4-0.8 ug/L. Mountain et al 3 used oral dexmedetomidine 4ug/kg and found that is comparable to 0.5mg/kg midazolam in reducing anxiety without any adverse effects. Hence we used oral midazolam at 0.5mg/kg and oral dexmedetomidine at 2 ug /kg to analyse the efficacy of the drugs. The usage of intravenous preparation of midazolam given orally mixed with a vehicle 33 in our study to make it palatable and the fact that it is more reliable and effective than the commercially available oral formulation is supported by the study of Brosius K K et al 27, where the study proved that the IV preparation mixed with a vehicle produced more reliable sedation and higher plasma level of the drug compared to the equivalent dose of commercially available preparation. In all the above cited study, oral formulations of dexmedetomidine and oral midazolam is prepared from preservative free iv injections, with compatible solutions. Volume of drug administered was adjusted to 0.2ml/kg(or 5ml) which was far lower than gastric fluid volume of 0.4ml/kg above which risk of aspiration increases. The age distribution was comparable in our study, with the mean age being 4.1 Years for midazolam and dexmedetomidine 3.8 years. Insignificant statistical difference was noted (p >0.05) between the two groups. The gender difference between the groups was not statistically significant (p>.05). Of 50 Children 37 males and 13 females for dexmedetomidine and for Midazolam 36 males and 14 females. The weight in kilograms of the children in both the groups was on an average 11.5 Kg without any significant difference (p>0.05). This favours that there is no significant statistical difference between both the groups in demographic profile. 40 children of midazolam group were in physical status I, and in spite of 10 in physical status II. In dexmedetomidine 43 children were in physical status I, only 7 in physical status II. There is no statistical significant difference between the Groups. (p =0.424). All children of both groups had accepted the oral premedication drugs without spitting the drug or disliking the taste. In terms of anxiety scale, in midazolam group 44 children were quiet and comfortable, 6 children were uneasy. Whereas in dexmedetomidine only 11 children were quiet, 26 were uneasy, 13 were anxious. There is significant difference between the groups in terms of anxiety scale. (p<0.01). In dexmedetomidine and midazolam 20 and 25 children were fully asleep, 26 and 21 children were drowsy, 4 children in both the group were awake respectively. There is no statistical significance between the groups (p=0.581) in terms of sedation scale. Mohamed et al 24, showed that oral midazolam with ketamine provided high sedation after 30 minutes of giving drug when compared to dexmedetomidine in the study. Singh et al 11, found midazolam to be the best sedative among three drugs (midazolam, trichlofos, promethazine). In terms of parental separation anxiety for midazolam groups 39 were easily separated from parents, 11 whimpers but reassuring, whereas in dexmedetomidine only

14 were easily separable, 33 whimpers but reassuring, 3 cries and not reassuring. None of children of both groups were clinging to parents. There is statistical high significant difference between the groups ($p < 0.001$). In mask acceptance behavior for the midazolam group of children 39 were calm and cooperative, 11 were anxious without resistance. Whereas in dexmedetomidine 14 were calm and cooperative, 34 were anxious without resistance, 2 were anxious with slight resistance. None of children were struggled against the mask. Aruna parameswari et al [12], have found a better mask acceptance with oral midazolam in their study. Mohamed et al [24] study found better mask acceptance with oral midazolam and ketamine group when compared to dexmedetomidine group. Suman Arora et al [35] showed midazolam was better in sedation, parental separation and mask acceptance when compared to clonidine and dexmedetomidine. The haemodynamic variables between the two groups were mean pulse rate in midazolam group (95.4/minute) and (94.5/minute) in dexmedetomidine group. Mean respiratory rate was (14.7/minute) in midazolam group and (14.2/minute) in dexmedetomidine group. Mean oxygen saturation in midazolam group was (99.5%) and for dexmedetomidine group was (99.2%). The intra operative haemodynamics had no significant variation from the preoperative values in both the groups ($p > 0.05$). There was no significant variation of heart rate, respiratory rate, blood pressure and oxygen saturation in both the groups intra operatively and post operatively. None of the children showed significant adverse effects in terms of hypotension bradycardia or respiratory depression.

LIMITATIONS

The peak onset of action of the two drugs are not the same but with the difference of 10-15 minutes. The dexmedetomidine takes 45 minutes for its onset whereas midazolam had taken 30 minutes for its action.

VI. Results

This study showed the safety and efficacy of midazolam and dexmedetomidine as an oral premedicant in paediatric age group. Midazolam showed better result in reducing anxiety, easy parental separation and excellent mask acceptance compared to dexmedetomidine group.

Midazolam and dexmedetomidine produced equal effect in terms of acceptance of premedication, sedation and haemodynamic stability.

VII. Conclusion

Based on our study “Randomized clinical trial of comparative study of oral dexmedetomidine versus oral midazolam as premedication in paediatric elective surgeries” we conclude that oral midazolam is a superior and safe premedicant in paediatric patients had faster onset of sedation, provided satisfactory sedation, lower anxiety score, easy parental separation and excellent mask acceptance as compared to dexmedetomidine.

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