Original Research Paper

Volume-8 | Issue-3 | March-2018 | PRINT ISSN No 2249-555X

Anesthesiology

COMPARISON OF INTRANASAL DEXMEDETOMIDINE AND INTRANASAL CLONIDINE AS SEDATIVE PREMEDICATION IN PAEDIATRIC ANAESTHESIA : A RANDOMIZED CLINICAL STUDY

Dr Shashank Maladkar — Senior Resident, McGann Hospital, Shimoga Institute of Medical Sciences, Shimoga.

Dr Karthik Shivani Lokeshappa* — Senior Resident, McGann Hospital, Shimoga Institute of Medical Sciences, Shimoga,*Corresponding Author

Dr Chennagiri Gangappa Ravindra — Associate Professor, McGann Hospital, Shimoga Institute of Medical Sciences, Shimoga.

ABSTRACT

BACKGROUND: Adequate premedication is an integral and important component of paediatric anaesthesia which should alleviate anxiety, allow comfortable separation of the child from the parent for smooth conduct of anaesthesia. Clonidine and dexmedetomidine are selective alpha-2 agonists with sedative and analgesic effects, which are effective through the nasal route. Both the drugs are being increasingly used in paediatric anaesthesia as a premedication and as an adjuvant in general as well as regional anaesthesia. We conducted a study to compare effectiveness of intranasal dexmedetomidine and clonidine as sedative premedication in paediatric patients undergoing various surgeries.

MATERIALS AND METHODS : After obtaining Institutional Ethical Committee clearance and parent's consent, a prospective, randomised, double-blinded clinical study was conducted in 80 children of ASA I and II, belonging to 2 - 10 years age, posted for various elective surgery. Group D (n= 40) received intranasal dexmedetomidine (2 mcg/kg) and Group C (n= 40) received clonidine (4 mcg/kg) instilled into both the nostrils. Sedation score (Ramsay), separation score, mask acceptance, recovery and vital parameters were recorded. Statistical analysis of data was done using IBM-SPSS version 21.0.

RESULTS : Mean sedation scores (± SD) were higher in Group D than in Group C at all time interval with a statistical significant difference at 25th and 30th minutes($P<0.05$). Separation scores were better with Group D than Group C ($P<0.05$). Mask acceptance scores were better with group C than group D. cardio-pulmonary parameters were similar in both the groups and no major adverse effects were noted.

CONCLUSION : Intranasal dexmedetomidine was associated with superior sedation levels and easier child-parent separation than clonidine and it appears to be a better choice for pre-anaesthetic medication.

KEYWORDS : premedication, clonidine, dexmedetomidine

INTRODUCTION

Extreme anxiety during induction of anaesthesia is associated with an increase of postoperative negative behavioural changes such as new onset enuresis, feeding difficulties, apathy, withdrawal, and sleep disturbances. Studies have indicated that up to 60% of all children undergoing surgery may present with negative behavioural changes at 2 weeks postoperatively. Preoperative anxiety also activates the stress response, leading to increased serum cortisol, epinephrine and natural killer cell activity.[1] So, relieving preoperative anxiety is of utmost importance for smooth conduct of anaesthesia in paediatric patients.

Preoperative Anxiety in children can be managed with non-pharmacological (behavioural) modalities and pharmacological modalities. Non-pharmacological modalities include the development of coping skills, modelling, and play therapy, operating room tour by viewing a picture or video and printed material and parental presence during induction of anaesthesia. Several drugs (pharmacological) have been tried to find the best sedative agent and the best route of administration of these drugs in children. So, a premedicant drug must have an acceptable, non-traumatic route of administration and should not add extra stress to the child. The most commonly used drugs are midazolam, ketamine, transmucosal fentanyl and/or meperidine.[1] Many studies have shown that intranasal route is an effective way to administer premedication to children. Recently, alpha-2 (α2) adrenergic agonists have been increasingly used as an option for premedication in children.[2]

Clonidine, a selective centrally acting partial alpha-2 agonist, a known anti-hypertensive agent has been successfully used through various routes in children like intravenous, oral and nasal routes. Because of its sedative and analgesic effects, it is gaining popularity in anaesthesiology as a preanaesthetic medication and as an adjuvant in general as well as regional anaesthesia.[3]

Dexmedetomidine is a potent, highly selective, and specific alpha-2 adrenoreceptor agonist that has sedative, anxiolytic and analgesic effects. It has a shorter half-life and its bioavailability is (72.6–92.1%) when administered via the nasal mucosa.[4] The sedative properties are largely due to effects on the locus ceruleus, producing a level of consciousness mimicking natural sleep. Nasal administration of dexmedetomidine is advantageous, as it is less invasive and anxiety provoking for the paediatric population and also it has a significantly lower risk of respiratory depression and hemodynamic changes.[5] These properties render it potentially useful for anaesthesia premedication.

We designed a study to compare the sedative effects of clonidine and dexmedetomidine when administered intranasally as preanaesthetic medication. The primary objectives were preoperative sedative effects, the ease of child-parent separation and satisfactory mask induction. The secondary objectives included hemodynamic changes and recovery profile.

MATERIAL AND METHODS

After approval from the Institutional Ethical Committee, a prospective randomized, double blinded, comparative study was conducted in 80 children undergoing elective surgical procedures, during February 2017 to December 2017. On the basis of the previous studies, a power calculation showed that 39 patients per group would be required for the study with 80% power. Therefore, 80 patients were selected for our study. We included 40 patients in each group during the period of our study.

Children of either sex in age group of 2 - 12 years, of American Society of Anaesthesiologists (ASA) physical status 1 and 2, were included in this study after obtaining written informed consent from the respective parents. The exclusion criteria were: Parental refusal for consent, children with a significant history of allergic disorders, ASA III or higher, and children with systemic illness like cardiac diseases, neurological, liver and renal disease.

Using a computer generated random number table, 80 children were enrolled into 2 groups.

Group D- Intranasal dexmedetomidine 2 mcg/kg (n=40)
Group C- Intranasal clonidine 4 mcg/kg (n=40)

An anaesthesia colleague who was not involved in observation or administration of anaesthesia for children prepared the study drugs. The drug was loaded in a graduated syringe and instilled in separate nostrils with the patient in supine position. The premedicant was administered approximately 30 minutes before induction of anaesthesia in the holding area in the presence of one of the parents.

Sedation score was assessed every 5 minutes from the administration of drug with the 6-point Ramsay sedation score[6] (Table No. 1) for a maximum of 30 minutes. When a sedation score of 3 or more was reached, the child was transferred to the operating room for induction and the time was noted. Child-parent separation was assessed according to a 4-point scale (Table No. 2).[7]

A standard technique for conduct of anaesthesia was maintained for all the patients. After placement of routine monitoring, anaesthesia was initiated with 70% nitrous oxide in oxygen and sevoflurane via transparent face mask and ease of induction was assessed by mask acceptance by the child according to a 4-point scale[8] (Table No. 3). Anaesthesia was maintained with oxygen, nitrous oxide and sevoflurane. At the end of surgery the child was allowed to wake up naturally and behaviour at awakening was recorded with a 4-point wake-up score[9] (Table No. 4). Pulse rate, blood pressure, electrocardiograph, SpO2 and respiratory rate were monitored continuously. Data were recorded and statistical analysis of data was done using IBM-SPSS version 21.0 by the following tests: Independent't' test and Chi-square test.

Tables

Table no.1 – Ramsay Sedation Scale

Patient anxious and agitated or restless or both	1
Patient co-operative, orientated, and tranquil	2
Patient responds to commands only	3
A brisk response	4
A sluggish response	5
No response	6

Table no.2 – Child Parent Separation Scale

Patient unafraid, cooperative, asleep	Excellent	1
Slight fear or crying, quite with reassurance	Good	2
Moderate fear, crying not quite with reassurance	Fair	3
Crying need for restraint	Poor	4

Table no.3 – Mask Acceptance Scale

Afraid, combative, crying,	Poor	1
Moderate fear of mask, not easily calmed,	Fair	2
Slight fear of mask, easily calmed	Good	3
Unafraid, cooperative, accepts mask easily	Excellent	4

Table no.4 – Wake up or Recovery Score

Calm and cooperative	1
Not calm but could be easily calmed	2
Not easily calmed, moderately agitated or restless	3
Combative, excited, disoriented	4

RESULTS

A total of 80 children were enrolled, 40 in each group. The demographic profiles of the patients of two groups were similar with respect to age, weight, sex and duration of anaesthesia. (Table 5)

Table no.5 – Demographic Profile between 2 Groups (Group C And Group D)

Demographic Characteristics	GROUP C (n=40)	GROUP D (n=40)	P
Age (years)	6.23±2.87	6.93±2.53	0.2503
Weight (kg)	21.35±5.34	23.25±5.65	0.1262
Male/Female (M/F)	32/8	27/13	0.3095
Mean duration of anaesthesia (min)	35.2±3.08	33.68±4.09	0.0634

In Group C, among 40 children 27 children achieved satisfactory sedation (67.5%) and in Group D, 38 children achieved satisfactory sedation (95%). Group D achieved a higher sedation levels than Group C at all-time intervals(except at 15th minute). There is a statistically significant difference in sedation scores between 2 groups at 25th minute (Group C-2.60±0.60, Group D-2.93±0.66 with a P= 0.0269) and 30th minute (Group C-2.95±0.90, Group D-3.53±0.81 with a P=0.0046). This indicates that Group D achieved superior and faster sedation levels than Group C (figure no.1 and table no.6).

Figure no.1 – Sedation Scores between 2 Groups (Group C and Group D)

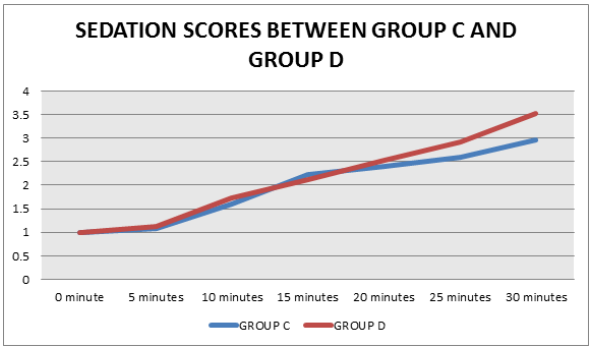


Table No.6- Sedation Scores, Parent Separation Scores, Mask Acceptance Scores and Wakeup Scores between 2 Groups (Group C And Group D)

PARAMETERS	GROUP C	GROUP D	P VALUE
SEDATION SCORE			
0 minute	1±0	1±0	--
5 minutes	1.07±0.33	1.13±0.33	0.4624
10 minutes	1.6±0.69	1.73±0.68	0.5657
15 minutes	2.23±1.07	2.13±1.06	0.4364
20 minutes	2.40±0.63	2.53±0.60	0.3668
25 minutes	2.60±0.60	2.93±0.66	0.0269*
30 minutes	2.95±0.90	3.53±0.81	0.0046*
PARENT SEPARATION SCORE	2.00±0.93	1.53±0.82	0.0177*
MASK ACCEPTANCE SCORE	2.85±1.31	2.78±1.33	0.8002
WAKE UP SCORE	1.50±0.51	1.53±0.51	0.8257

*P<0.05

Regarding child-parent separation scores, there is a statistically significant difference between the 2 groups- Group D (mean score of 1.53 with an SD of 0.82) and Group C (mean score of 2.00 with an SD of 0.93) with a P value of 0.0177. The scores are better with Group D than with Group C.

Mask acceptance scores were better with group C than group D. But this difference is statistically not significant. Both the groups achieved similar wakeup scores which is statistically not significant. Heart rate, mean blood pressure and oxygen saturation was similar in both the groups at different time intervals (figure no.2 and 3).

Figure no.2 - Pulse rate Between 2 Groups (Group C and Group D)

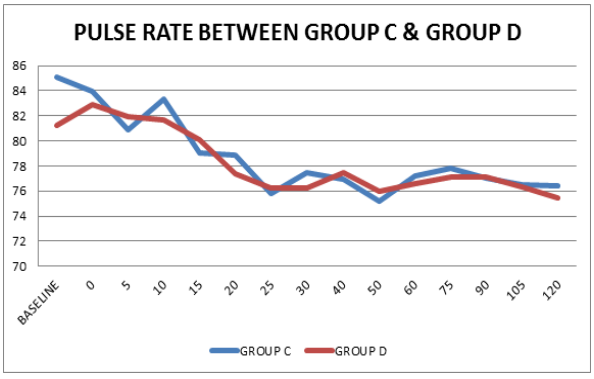
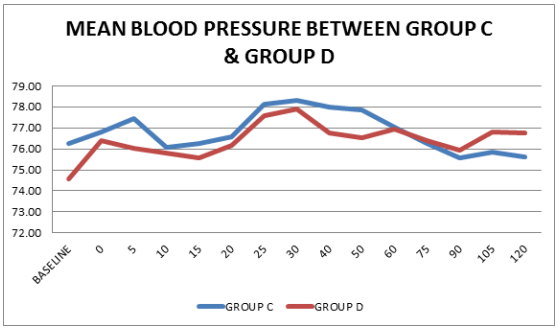


Figure no.3 – Mean Blood Pressure between 2 Groups (Group C And Group D)



DISCUSSION

In our study, we compared effects of intranasal dexmedetomidine and intranasal clonidine as a sedative premedication in children undergoing surgery. We found premedication with 2 mcg/kg of intranasal dexmedetomidine and 4 mcg/kg of intranasal clonidine to be equally effective in decreasing anxiety at parental separation.

Dexmedetomidine is a newer selective alpha-2 agonist with a site of action at the locus ceruleus. It inhibits presynaptic release of norepinephrine that is responsible for its sedative and hypnotic effects. The analgesic effects occur on account of activation of alpha-2 adrenoceptor in the descending medulla spinal noradrenergic pathway. Bradycardia and hypotension occur on account of post-synaptic activation of alpha-2 receptors in the central nervous system. The finding of electroencephalogram activity similar to natural sleep supports the easy arousability from its effects.[10] Studies by Sidhu et al[2] and G.Ulufer Sivrikaya et al[11] showed that intranasal dexmedetomidine 2 mcg/kg produced satisfactory anxiolysis at 30 minutes.

Clonidine is increasingly used in paediatric population as a sedative and analgesic because of its central α2-adrenoceptor agonist action. It has been successfully used orally, intravenously, intrathecally, epidurally and intramuscularly in children in a dose range of 1-5 mcg/kg. It has several applications in paediatric anaesthesia as a premedication and as an adjuvant in general as well as regional anaesthesia.[12] Studies by Mitra S et al[12], Mukherjee, et al[13] and Nicole Almeander et al[14] showed that clonidine administered via nasal route at a dose of 4 mcg/kg produced satisfactory anxiolysis at 30 minutes.

Atropine intranasally (20 mcg/kg) was given to prevent reduction in heart rate associated with clonidine and dexmedetomidine. Nasal atropine has been shown to reduce nasal secretions and mucociliary clearance, which might favour nasal drug absorption.[2,12]

In our study, the proportion of children who achieved satisfactory sedation were more with dexmedetomidine as compared to that of clonidine and the difference was statistically significant ($P < 0.05$). In a study done by Yuen et al,[9] where two different doses of intranasal dexmedetomidine (D1 and D0.5 Group) and oral midazolam were compared, it was found that 75% of children in D1 Group and 59.4% in D0.5 Group attained satisfactory sedation at 60 min. In another study by G.Ulufer Sivrikaya et al[11] et al 91.4% children premedicated with dexmedetomidine were satisfactorily sedated. S.A.sheta et al[15] in their study, found that about 77.8% children achieved satisfactory sedation. In study by A. Akin et al[16] 79.9% children premedicated with dexmedetomidine were satisfactorily sedated. Gupta et al[17] found in their study that 80% children premedicated with dexmedetomidine were satisfactorily sedated. But in our study about 95% children (38 out of 40) achieved satisfactory sedation. The difference in scoring system between various studies might have contributed to this difference.

In a study by Sidhu et al[2] the proportion of patients with satisfactory sedation after intranasal premedication was 25.7%. Mitra et al[12] in their study found that 100% children premedicated with intranasal clonidine achieved satisfactory sedation. But in our study, only 67.5% children (27 out of 40) in clonidine group achieved satisfactory sedation.

Clonidine has slow onset of action and delayed peak effect when given by oral or intranasal route. So, fewer patients achieved satisfactory anxiolysis and sedation at 30 min in clonidine group as compared to dexmedetomidine group. The explanation of better anxiolysis and sedation with dexmedetomidine goes with difference in pharmacokinetics of two drugs as dexmedetomidine has 8–10 folds greater α2 selectivity than clonidine. The improved sedative and analgesic properties of dexmedetomidine as compared to clonidine are attributed to its higher affinity for α-2A adrenoceptor subtype.[2]

In our study, both the groups achieved satisfactory recovery in all the children (100%). Heart rate, oxygen saturation and blood pressure were similar in both the groups at different time intervals. There were no adverse effects like nausea, vomiting, nasal stinging, shivering or bradycardia.

Limitation

However, the present study had certain limitations. Longer premedication time (around 45 minutes) would have allowed increased proportion of children with greater sedative effect in both groups, but longer time was impractical in our hospital settings where there is rapid turnover of patients.

CONCLUSION

In our study, we found that premedication with 2 mcg/kg of intranasal dexmedetomidine and 4 mcg/kg of intranasal clonidine to be equally effective in decreasing anxiety at parental separation. Dexmedetomidine was associated with superior sedation levels and easier child-parent separation than clonidine. So we conclude that intranasal dexmedetomidine appears to be a better choice for pre-anaesthetic medication.

REFERENCES

1. McCann, M. E., & Kain, Z. N. (2001). The management of preoperative anxiety in children: an update. Anesthesia & Analgesia, 93(1), 98-105.
2. Sidhu, G. K., Jindal, S., Kaur, G., Singh, G., Gupta, K. K., & Aggarwal, S. (2016). Comparison of intranasal dexmedetomidine with intranasal clonidine as a premedication in surgery. The Indian Journal of Pediatrics, 83(11), 1253-1258.
3. Dahmani, S., Brasher, C., Stany, I., Golmard, J., Skhiri, A., Bruneau, B., ... & Murat, I. (2010). Premedication with clonidine is superior to benzodiazepines. A meta analysis of published studies. Acta anaesthesiologica Scandinavica, 54(4), 397-402.
4. Mostafa, M. G., & Morsy, K. M. (2013). Premedication with intranasal dexmedetomidine, midazolam and ketamine for children undergoing bone marrow biopsy and aspirate. Egyptian Journal of Anaesthesia, 29(2), 131-135.
5. Behrle, N., Birisci, E., Anderson, J., Schroeder, S., & Dalabih, A. (2017). Intranasal Dexmedetomidine as a Sedative for Pediatric Procedural Sedation. The Journal of Pediatric Pharmacology and Therapeutics, 22(1), 4-8.
6. Ramsay, M. A. E., Savege, T. M., Simpson, B. R. J., & Goodwin, R. (1974). Controlled sedation with alphaxalone-alphadolone. British medical journal, 2(5920), 656.
7. Mitchell, V., Grange, C., Black, A., & Train, J. (1997). A comparison of midazolam with trimeprazine as an oral premedicant for children. Anaesthesia, 52(5), 416-421.
8. Chaudhary, S., Jindal, R., Girotra, G., Salhotra, R., Rautela, R. S., & Sethi, A. K. (2014). Is midazolam superior to triclofos and hydroxyzine as premedicant in children?. Journal of anaesthesiology, clinical pharmacology, 30(1), 53.
9. Yuen, V. M., Hui, T. W., Irwin, M. G., & Yuen, M. K. (2008). A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. Anesthesia & Analgesia, 106(6), 1715-1721.
10. Kumar, L., Kumar, A., Panikkaveetil, R., Vasu, B. K., Rajan, S., & Nair, S. G. (2017). Efficacy of intranasal dexmedetomidine versus oral midazolam for paediatric premedication. Indian journal of anaesthesia, 61(2), 125.
11. Sivrikaya, G. U. (2015). Intranasal Dexmedetomidine Versus Midazolam Premedicatıon in Paediatric Patients: A Prospec-tive Study. EC Anaesthesia, 2, 139-147.
12. Mitra, S., Kazal, S., & Anand, L. K. (2014). Intranasal clonidine vs. midazolam as premedication in children: a randomized controlled trial. Indian pediatrics, 51(2), 113-118.
13. Mukherjee, S., Ray, M., Ray, A., Khanra, M., Mandal, P. K., & Pal, R. (2010). Clonidine premedication for paediatric patients: A comparison of the oral & nasal route. Journal of Anaesthesiology Clinical Pharmacology, 26(3), 319-322.
14. Almenrader, N., Passariello, M., Coccetti, B., Haiberger, R., & Pietropaoli, P. (2007). Steal‐induction after clonidine premedication: a comparison of the oral and nasal route. Pediatric Anesthesia, 17(3), 230-234.
15. Sheta, S. A., Al‐Sarheed, M. A., & Abdelhalim, A. A. (2014). Intranasal dexmedetomidine vs midazolam for premedication in children undergoing complete dental rehabilitation: a double‐blinded randomized controlled trial. Pediatric Anesthesia, 24(2), 181-189.
16. Akin, A., Bayram, A., Esmaoglu, A., Tosun, Z., Aksu, R., Altuntas, R., & Boyaci, A. (2012). Dexmedetomidine vs midazolam for premedication of pediatric patients undergoing anesthesia. Pediatric Anesthesia, 22(9), 871-876.
17. Gupta, A., Dalvi, N. P., & Tendolkar, B. A. (2017). Comparison between intranasal dexmedetomidine and intranasal midazolam as premedication for brain magnetic resonance imaging in pediatric patients: A prospective randomized double blind trial. Journal of anaesthesiology, clinical pharmacology, 33(2), 236.