# DEXMEDETOMIDINE REDUCES HAEMODYNAMIC VARIATION IN PAEDIATRIC PATIENTS DURING SURGERY

**Badri Prasad Das[1], Ram Badan Singh[2,*], Rajiv Kumar Dubey[3], Yashpal Singh[4]**

[1]Resident, [2]Associate Professor, [3,4]Assistant Professor, Department of anesthesiology, IMS, BHU Varanasi – 221005

***Corresponding Author:**
E-mail: rambadan.vns@gmail.com

**ABSTRACT**

**Background:** *Anaesthesia and surgery (thoracic and upper abdominal) are very stressful and painful and pain if not relived adequately it may lead to hemodynamic instability with respiratory compromise and increased complications in intra-operative and Post-operative period. The common agents available for sedation and analgesia includes opiates and benzodiazepines. Use of these agents have side effects, including respiratory and cardiovascular depression. Dexmedetomidine HCl, a highly potent α2-adrenergic agonist, have sedative, analgesic, hypnotic and anxiolytic effects without causing respiratory depression.*
**Objective:** *The objective of this study is to find out safe and effective adjuvant of analgesic and sedative drug which can reduce stress of anesthesia and surgery and provide stable hemodynamics in intra operative period with rapid recovery from anesthesia.*
**Material and Methods:** *After ethical clearance and informed consent 120 eligible paediatric patients aged 2-10 years, of either sex, ASA physical status I and II scheduled for thoracic and upper abdominal surgeries were allocated randomly into 2 groups (DEX group and NS group) each containing 60 patients. DEX group received Dexmedetomidine 1mcg/kg (loading) (made to 20ml) slow IV injection over 20minutes, before inducing anaesthesia, followed by 0.5mcg/kg/hour (maintenance) peri & post-operatively over 6hours through infusion pump. NS Group received only normal saline 20ml slow IV injection over 20minutes, before inducing anaesthesia and continued infusion in same way as DEX group. General anaesthesia was induced using a standard dosage protocol. Hemodynamic parameters monitored and recorded at frequent interval. Statistical analysis was done and data were analysed.*
**Results:** *Stress induced Hemodynamic response during laryngoscopy, intubation, surgery and extubation was significantly less in Dex group patients with lesser halothane consumption and rescue analgesic requirement ( $p<0.05$) in intra operative period.*
**Conclusion:** *Use of IV Dexmedetomidine peri-operatively, significantly decreases haemodynamic response of stress related to anaesthesia and surgery. It also decreases sedative and analgesic requirements with good pain relief and stable haemodynamics with lower post- operative complications.*

**Key Words:** *Dexmedetomidine, Anesthesia, Surgery, Haemodynamic response.*

## BACKGROUND

Anaesthesia, thoracic and upper abdominal surgeries are very stressful and painful because movement of operated site with respiration in post-operative period. .If pain is not relived adequately it may lead to increased sympathetic response and hemodynamic instability with respiratory compromise and increased complications in intra-operative and Post-operative period. Pain may have long-term negative effects on pain sensitivity, immune functioning, neurophysiology, attitudes, and health related behaviors[1-3]. The common agents available for sedation and analgesia includes opiates and benzodiazepines. The use of these agents have side effects, including respiratory and cardiovascular depression. Dexmedetomidine HCl, a highly potent α2-adrenergic agonist, have sedative, analgesic, hypnotic and anxiolytic effects without causing respiratory depression. It may be helpful in reducing requirement of other sedative and analgesics for a calm, comfortable and cooperative state.

## OBJECTIVE

The objective of this study is to find out safe and effective adjuvant of analgesic and sedative drug which can reduce stress of anesthesia and surgery and provide stable hemodynamics in intra operative period with rapid recovery from anesthesia in paediatric patients..

## MATERIAL AND METHODS

After approval from institute ethical and research committee, a double blind randomized placebo controlled study was performed which included 120 ASA grade 1 and 2 paediatric patients age between 2 to 10 years who were scheduled for thoracic and upper abdominal surgeries. Patients with history of bronchial asthma, seizures, cardio-vascular disorders were excluded from study. After written informed consent from parents or guardians, all patients were randomly allocated into 2 groups (DEX group and NS group) each group containing 60 patients. All patients were pre medicated with oral midazolam 0.2mg/kg, 2 hour before surgery. On arrival to operating room, pulse Oximetry, ECG and noninvasive blood pressure were recorded for baseline values. Patients allocated in DEX group received Inj. Dexmedetomidine 1 µg/kg (loading, made in 20 ml) slow IV over 20 min, 20 min before induction; followed by 0.5 µg/kg/hour (maintenance) in perioperative period for 6 hours through infusion pump. Similarly, patients in NS group received Inj Normal Saline 20 ml (loading) slow IV over 20 min, before induction; followed by 0.5 ml/kg/hour (maintenance) in perioperative period for 6 hours through infusion pump. Inj Ondensetron 0.1mg/kg IV and Inj Fentanyl 1.5mcg/kg given slowly IV. General anaesthesia was induced with Inj Propofol 2mg/kg slow IV till loss of verbal contact and Inj Vecuronium 0.1mg/kg IV was given for neuromuscular blockade. After 3 minute of induction, the child was intubated with appropriate size endo-tracheal tube and anaesthesia was maintained with Halothane 0.4% to 1.0% in 50% Nitrous oxide + 50% Oxygen. All patients were ventilated with appropriate respiratory rate to maintain end-tidal CO2 at 35-40 mm Hg. Intra-operative pain assessed by hemodynamic response and treated with Inj Tramadol 2mg/kg slow IV and Inj Paracetamol 15mg/kg slow IV over 15 min as rescue analgesia. After induction of anesthesia, hemodynamics were recorded and maintained near baseline value using 0.4 to 1.0% halothane, fluid and other drugs. After surgery neuromuscular blockade was antagonized with Inj Neostigmine 50µg/kg and Inj Glycopyrrolate 10µg/kg. After confirming adequate spontaneous respiratory effort, the patients were extubated and shifted to post-anaesthesia care unit (PACU). Intra operative HR, SBP, DBP, MBP, SpO2, end-tidal carbon-dioxide (EtCO2) and Halothane concentration was recorded at 0 min, 10 min, 20 min of loading of Inj dexmedetomidine, at induction of anesthesia, 1 min after induction, 5 min after induction, at tracheal intubation, 1 min after intubation, 5 min after intubation; at skin incision, thereafter every 15 min throughout the procedure, at wound closure; at extubation, 1 min after extubation, 5 min after extubation, and 2 hourly in post-operative period for 6 hours. After arrival in PACU, subjective and objective assessment of pain, and adverse events were recorded 2hourly till 6hrs of post-operative period. Use of rescue analgesia if any, were noted. The data were analysed using different statistical tests.

## OBSERVATIONS

All demographic parameters were comparable in both the groups (table 1). Both groups had various thoracic and upper abdominal surgical procedures (table 2). Baseline mean HR and Mean BP were comparable between two groups, but after 20 minutes of starting infusion HR and Mean BP in DEX group were significantly lower than NS group and continued to be lower throughout the anesthetic procedure ($P<0.05$) (figure 1, 2). The 10.52% decrease of mean HR from baseline during induction was observed in DEX group and 10.94% in NS group with statistically insignificant difference (P value = 0.35) (table 3). There was decrease of mean MBP from baseline during induction less in DEX group (4.33%) as compared to NS group (7.66%) with very minimal but statistically significant difference (p value = 0.04). During intubation, there was increase in mean HR and MBP from baseline but was less in DEX group as compared to NS group with P value being highly significant ($P <0.001$). Intra-operatively, DEX group showed significantly lower mean HR and MBP as compared to NS group at all time. The mean HR and MBP in DEX group showed a 6% and 8% fall as compared to 3.7% and 3.6% rise in NS group from baseline ($P<0.001$). The halothane consumption intra-operatively was significantly reduced to almost half due to dexmedetomidine use, ($P<0.001$) figure 3.

Mean halothane consumption in NS group was around 0.8% conc. while that in DEX group was around 0.4% conc. (P<0.001). In intra-operative period, in NS group, more than half patients required rescue analgesia around 30-45 min of start of operation and in the first 2 hours of post-operative period (figure 4). Whereas, in DEX group, significantly less number of patients required rescue analgesia in intra and post-operative period. There was a significant reduction in the requirement of rescue analgesia with dexmedetomidine use (33.33% intra operatively and 26.675 post operatively in DEX group against 100% of patients in NS group, both intra- and post-operatively) P<0.001. The most common complication noted with DEX group was hypotension (26.67%) followed by bradycardia (20%) during both intra- and post-operative period figure 5. These complications were significant clinically and statistically, but promptly managed with Inj Atropine and Inj Mephentermine. In NS group, the most common complication was post-operative pain (100%), followed by PONV (46.67%), shivering (26.67%) and delirium (16.67%). These were significantly lower with dexmedetomidine use. (Figure 5). The duration of recovery was similar in both groups.

**Table 1: Distribution of Age, weight, sex and anesthetic duration and their statistical comparison.**

| Variable | DEX | NS | P-value |
|---|---|---|---|
| Age (yrs), Mean ± SD | 6.33±2.62 | 6.15±2.56 | 0.985 |
| Weight(kg), Mean ± SD | 20.60±7.30 | 20.47±7.25 | 0.920 |
| Sex, (No.)<br>Male<br>Female | <br>32<br>28 | <br>30<br>30 | 0.714 |
| Anaesthesia duration (min) | 81 ± 10.1 | 72±11.4 | 0.27 |

**Table 2: pathological diagnosis of test and study groups.**

| DIAGNOSIS | DEX | NS | TOTAL |
|---|---|---|---|
| **ABDOMINAL PATHOLOGIES** | | | |
| Cong. hypertrophic pyloric stenosis | 6 | 5 | 11 |
| Biliary atresia | 3 | 3 | 6 |
| Duodenal atresia | 4 | 5 | 9 |
| Hirschprung disease | 6 | 5 | 11 |
| Intestinal obstruction | 5 | 4 | 9 |
| Hydatid cyst (hepatic) | 4 | 6 | 10 |
| Umbilical hernia | 7 | 5 | 12 |
| Renal mass | 6 | 6 | 12 |
| **THORACIC PATHOLOGIES** | | | |
| Diaphragmatic hernia | 4 | 5 | 9 |
| Esophageal atresia | 6 | 6 | 12 |
| Hydatid cyst (lung) | 2 | 3 | 5 |
| Cong. lobar emphysema | 4 | 4 | 8 |
| Cystic adenomatoid lung malformation | 3 | 3 | 6 |
| **TOTAL** | 60 | 60 | 120 |

**Table 3: % change in haemodynamic parameters**

| % change | DEX | NS | P value |
|---|---|---|---|
| **INDUCTION** | | | |
| ΔHR | 10.52 | 10.94 | P=0.35 |
| ΔSBP/DBP(MBP) | 7.61/3.68(4.33) | 8.55/13.36(7.66) | P=0.04 |
| **sINTUBATION** | | | |
| ΔHR | 19.73 | 22.72 | P<0.001 |
| ΔSBP/DBP(MBP) | 11.13/13.83(9.56) | 23.95/30.26(20.05) | P<0.001 |
| **EXTUBATION** | | | |
| ΔHR | 18.69 | 21.95 | P<0.001 |
| ΔSBP/DBP(MBP) | 14.98/8.97(9.62) | 16.67/12.65(10.39) | P<0.001 |

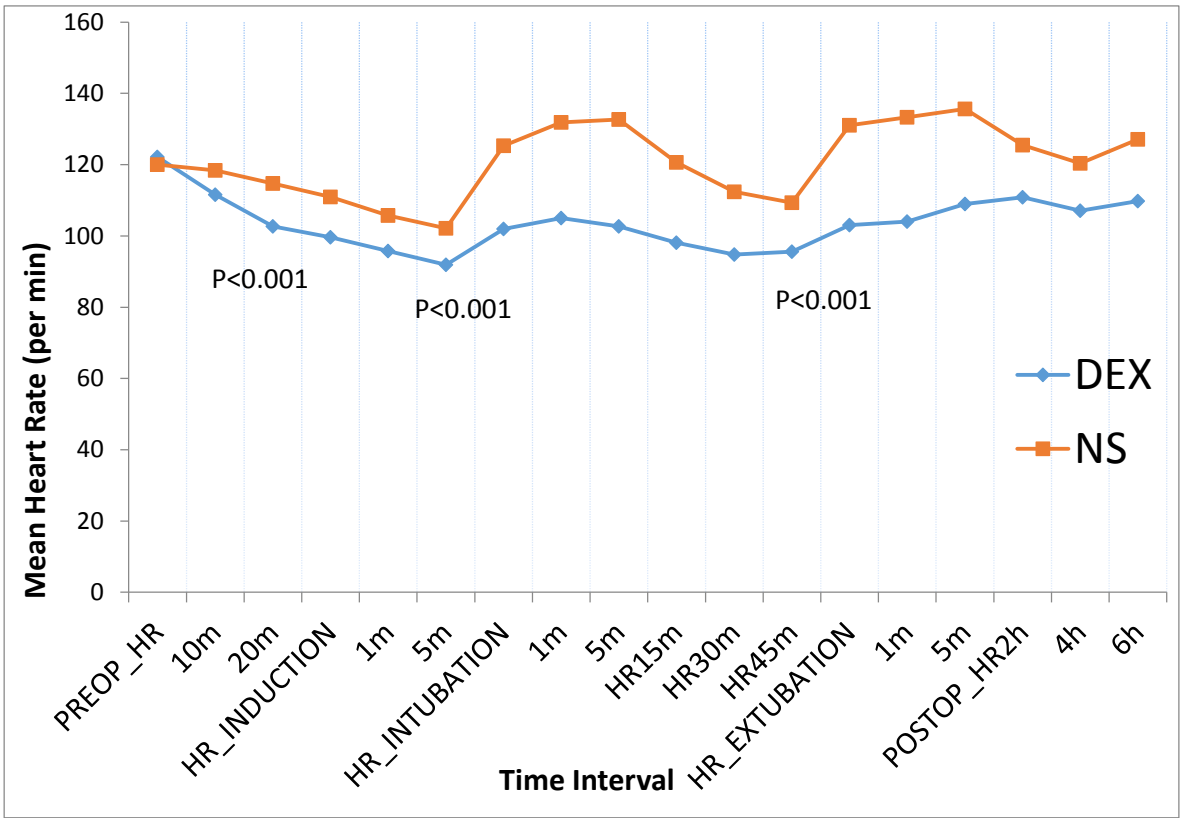


**Figure 1: Graphical comparison of mean HR**

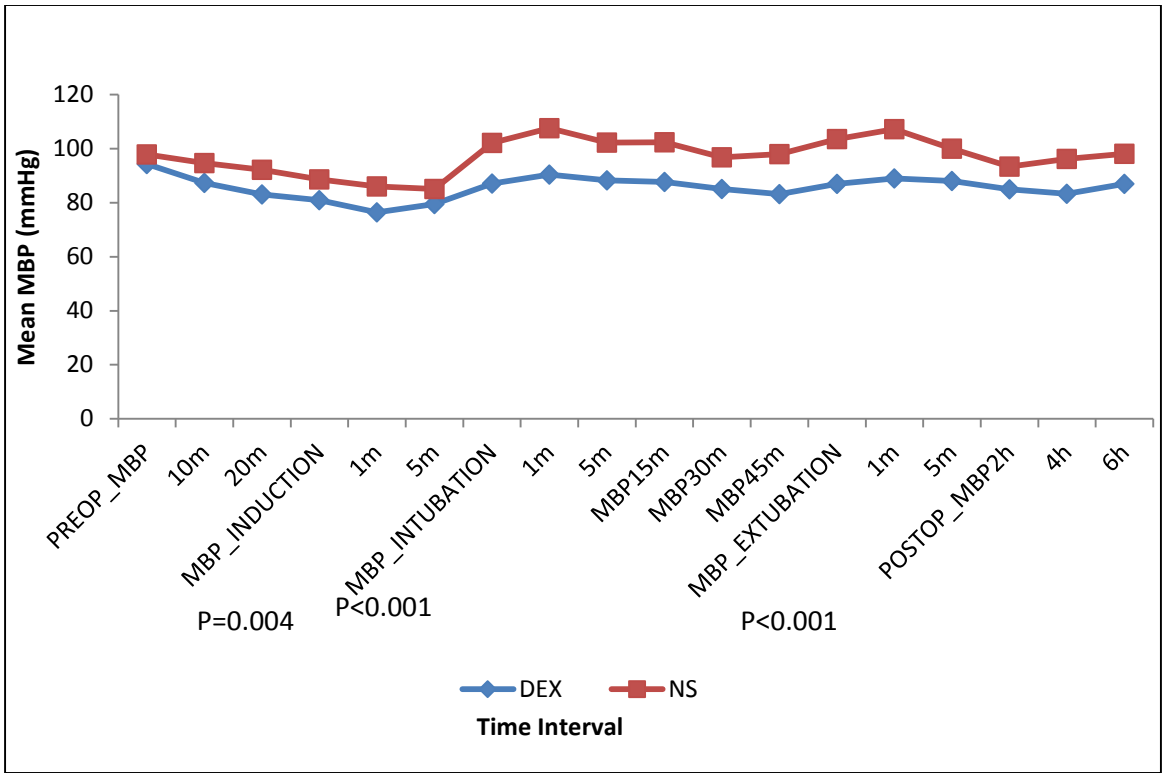


**Figure 2: Graphical comparison of mean MBP**

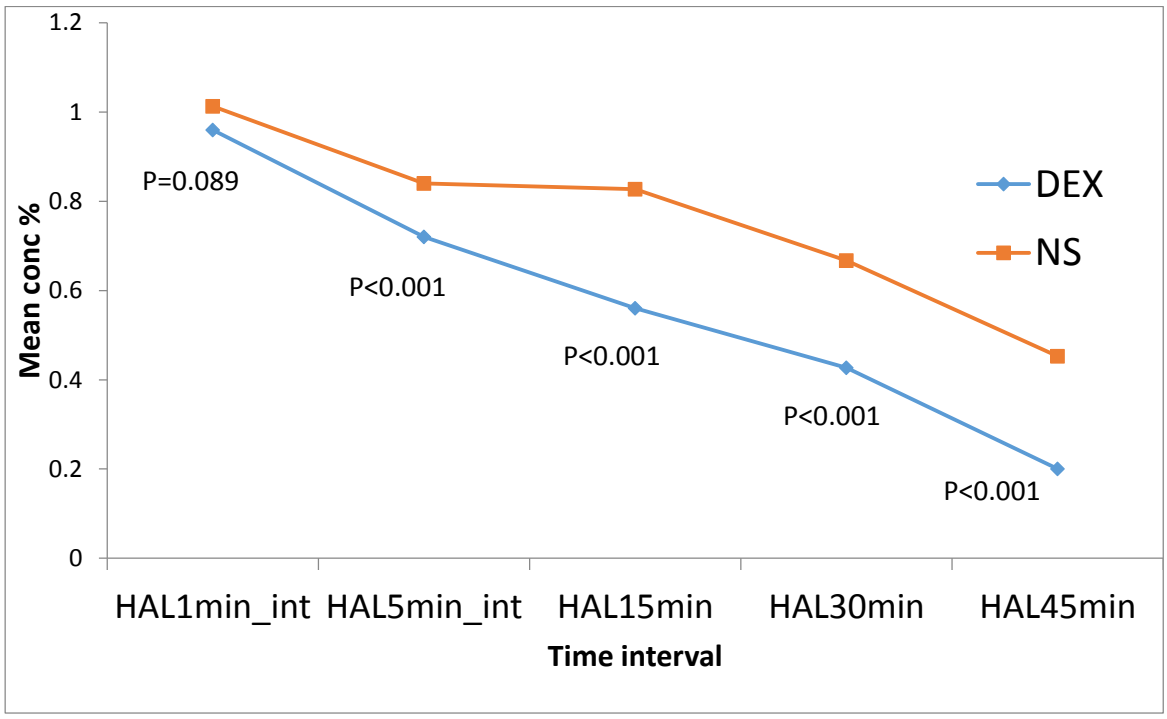


**Figure 3: Graphical comparison of halothane consumption**

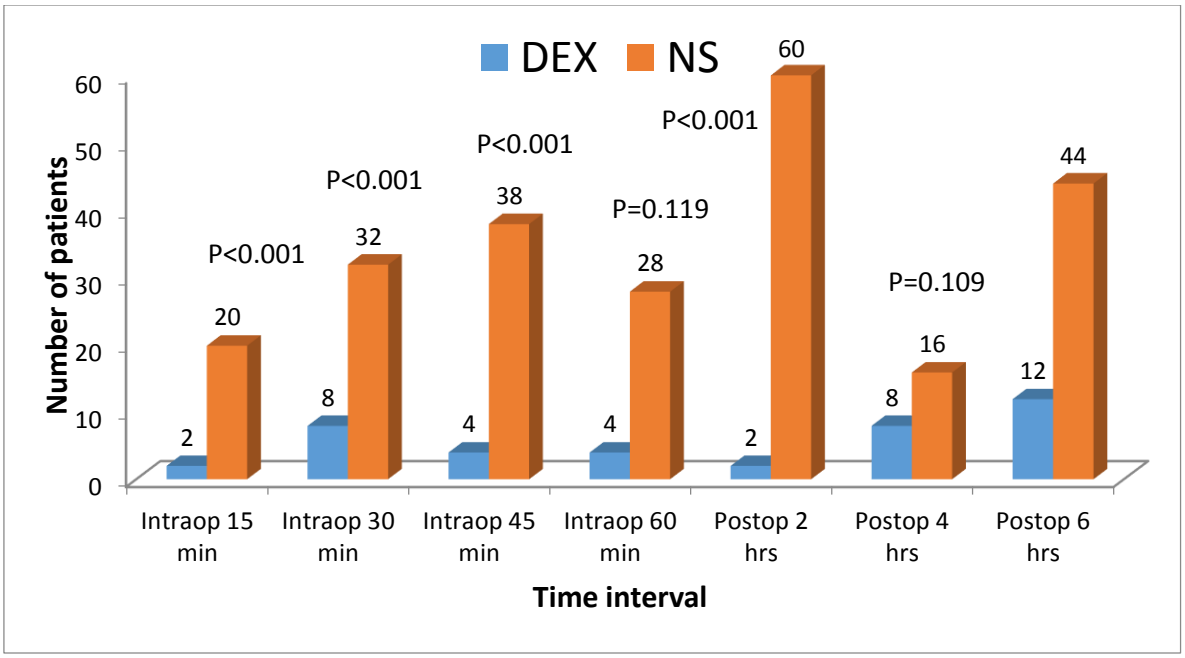


**Figure 4: Graphical comparison of rescue analgesia requirements**

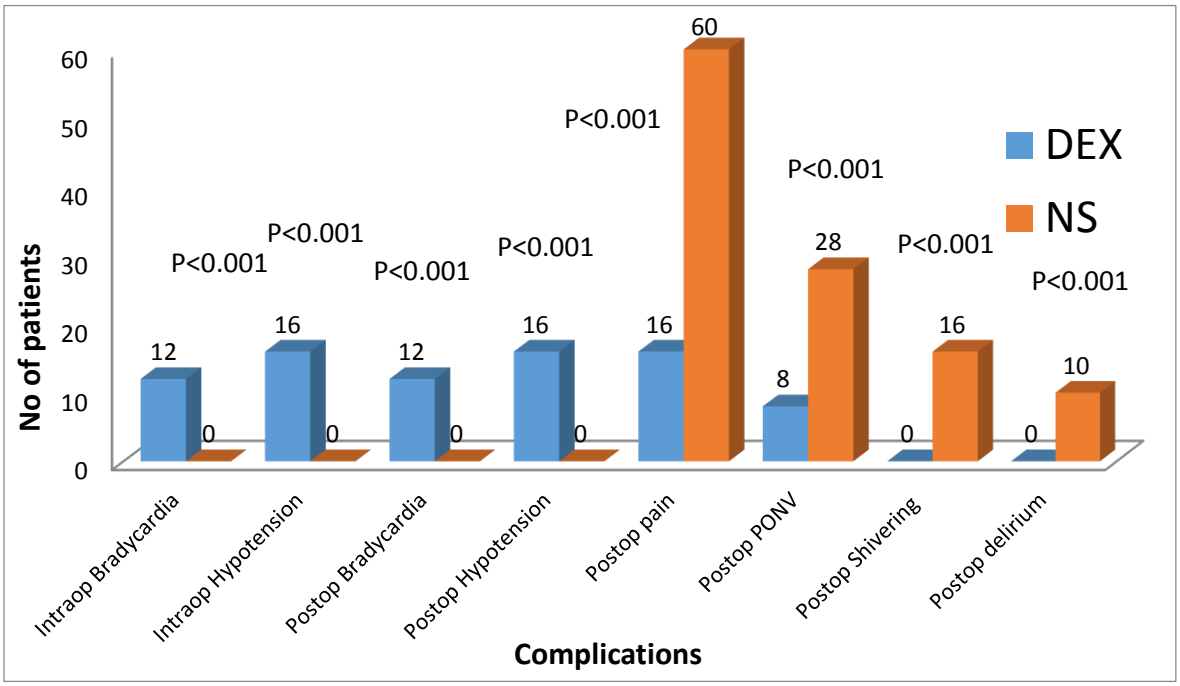


**Figure 5: Graphical comparison of complications**

## DISCUSSION

Dexmedetomidine is a highly potent agonist at the α2-adrenergic receptor (8 times more selective for α2receptor than clonidine)[4,5]. This increased selectivity and shorter half-life of 2-3hours results in more predictable, effective sedation and analgesia with fewer side effects [6]. It is helpful in reducing sedative/analgesic use allowing a calm, comfortable, and cooperative state. Dexmedetomidine is safe even in doses high enough to cause unresponsiveness [7-17] and inhibits release of catecholamines from the sympathetic nerve terminals by augmentation of a vasoconstrictive effect [18,19]. Joseph D. Tobias et al used dexmedetomidine intravenous infusions in infants and children undergoing cardiac surgeries and emphasized the safety and

benefit of dexmedetomidine in managing pediatric patients [20-22]. Bajwa Sukhminder Jit et al (2012) studied attenuation of pressor response and dose sparing of opioids and anaesthetics with pre-operative dexmedetomidine and concluded that dexmedetomidine not only decreased the magnitude of stress response to intubation, surgery and extubation but also decreased the dose of opioids and isoflurane in achieving an adequate analgesia and anaesthesia, respectively [23].

In our study, a dose of 1 µg/kg of dexmedetomidine reduced the haemodynamic responses to laryngoscopy and tracheal intubation. And, after a maintenance dose of 0.5 µg/kg/hr dexmedetomidine peri-operatively, there was significant fall in hemodynamic parameters (HR, BP) at all-time interval and this suppressed hemodynamic state was similar with previous studies and maintained without much problem throughout the intra-operative period. During reversal, the extubation response was reduced but not completely abolished. There was no significant delay in extubation and the emergence from anaesthesia, and recovery profile was clinically and statistically comparable in both the groups. This could be due to activation of Post synaptic α2-adrenoceptors[24,25] leading to dose dependent reduction[26] in level of endogenous plasma catecholamines, bradycardia and hypotension secondary to sympathetic inhibition of medullary vasomotor center and augmentation of vagal activity[27,28]. Also, the requirement of inhalational anaesthetic for maintenance of anaesthesia during the entire surgical procedure was markedly reduced to nearly half with use of dexmedetomidine at a maintenance dose of 0.5 µg/kg/hour (mean halothane concentration used was 0.4%).

Chrysostomou C et al used dexmedetomidine in infants undergoing cardiac surgeries and emphasized the cardiostable property of dexmedetomidine[29,30]. Tokuhira N, Atagi K, Shimaoka H, et al. compared dexmedetomidine to standard analgesic/sedative combinations after Fontan surgery and concluded that the lack of respiratory depression with dexmedetomidine may decrease the risk for elevated pulmonary vascular resistance and improve cardiac function, making it a useful option for sedation after Fontan surgery[31]. Ahmed M. Mukhtar et al and Joseph D. Tobias et al used the drug in paediatric cardiac surgeries with the same results[32,22]. Our study also revealed that a maintenance dose of dexmedetomidine 0.5 µg/kg/hr decreased the rescue analgesic requirements in intra-operative period, though it could not be regarded as a sole analgesic. Only 33.33% of patients in DEX group required rescue analgesia against all patients in NS group ($P<0.001$). The most common complication noted with dexmedetomidine was bradycardia (20% in DEX group) and hypotension (26.67% in DEX group) both during intra- and post-operative period ($P<0.001$) which promptly responded to Inj Atropine and Inj Mephentermine, respectively.

Earlier studies had demonstrated a transient increase in HR and MBP initially during the administration of dexmedetomidine infusion, which was followed by a decrease[15]. A similar kind of phenomenon was encountered during the present study as a transient increase in HR and MBP for 3–5 min was observed in 2 patients after the start of dexmedetomidine infusion and was probably due to the vasoconstriction effect of dexmedetomidine appearing earlier than the central sympathetic action. α2B- adrenergic receptors in peripheral arteries are responsible for the initial short hypertensive phase while subsequent hypotension is mediated by post-synaptic α2A- adrenergic receptors on medullary vasomotor center[13,33]. This biphasic response on hemodynamic parameters was evoked only after administering it rapidly or with a relatively large dose (>1000 µg/kg). This direct effect on the peripheral vascular smooth muscle usually lasted for up to 10 min. Although it had significant side-effects of bradycardia and hypotension, dexmedetomidine could be relatively a safe cardio stable drug.

**CONCLUSION**

With this study we concluded that, perioperative dexmedetomidine, when administered intravenously as an adjuvant to general anaesthesia, in paediatric patients undergoing thoracic and upper abdominal surgeries, reduces stress responses to noxious stimuli and maintained hemodynamic parameters within acceptable range.

**BIBLIOGRAPHY:**


1. Young KD. Pediatric procedural pain Ann Emerg Med. 2005 Feb;45(2):160-71
2. Stevens B, Johnston C, Petryshen P, Taddio A. Premature infant pain profile: Development and initial validation. Clinical Journal of Pain. 1996;12:13–22.
3. Fitzgerald M, Beggs S. The neurobiology of pain: developmental aspects. Neuroscientist. 2001;7:246-57.4.
4. Scholz J, Tonner PH. Alpha-adrenoceptor agonists in anaesthesia: a new paradigm. Curr Opin Anaesthesiol 2000; 13: 437-42.
5. Kaur M, Singh PM. Current role of dexmedetomidine in clinical anesthesia and intensive care. Anesth Essays Res 2011;5:128-33.
6. Philipp M, Brede M, Hein L. Physiological significance of alpha(2)-adrenergic receptor subtype diversity: one receptor is not enough. Am J Physiol Regul Integr Comp Physiol 2002;283:R287-95.
7. Lam SW, Alexander E, Sulsa GM. DRUG UPDATE: Dexmedetomidine Use in Critical Care; AACN Advanced Critical Care 2008;19:113-20.
8. Tobias JD: Dexmedetomidine: Applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med 2007;8:115-31.
9. Deutsch E, Tobias JD: Hemodynamic and respiratory changes following dexmedetomidine administration during general anesthesia: Sevoflurane vs desflurane. Paediatr Anaesth 2007;17:438-44.
10. Blaine ER, Brady KM, Tobias JD: Dexmedetomidine for the treatment of postanesthesia shivering in children. Paediatr Anaesth2007;17:341-6.
11. Isik B, Arslan M, Tunga AD, et al: Dexmedetomidine decreases emergence agitation in pediatric patients after sevoflurane anesthesia without surgery. Paediatr Anaesth 2006;16:748-753.
12. Hossain M, Rajakumaraswamy N et al., Dexmedetomidine produces its neuroprotective effect via the alpha 2A-adrenoceptor subtype. Eur J Pharmacol 2004;502:87-97.
13. Shukry M, Miller JA. Update on dexmedetomidine: Use in non-intubated patients requiring sedation for surgical procedures. Ther Clin Risk Manag 2010;6:111-21.
14. Yazbek-Karam VG, Aouad MM. Perioperative uses of dexmeditomidine. MEJ Anaesth 2006;18:1043-56.
15. Farag E, Argalious M, Sessler DI, Kurz A, Ebrahim ZY, Schubert A. Use of a2 Agonists in Neuroanesthesia: An Overview. Ochsner J 2011;11:57-69.
16. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382-94.
17. Shehabi Y, Botha JA, Ernest D, Freebairn RC, Reade M, Roberts BL, et al. Clinical application, the use of dexmedetomidine in intensive care sedation. Crit Care Shock 2010;13:40-50.
18. Bergese SD, Candiotti KA, Bokesch PM, Zura A, Wisemandle W, Bekker AY. WAKE Study Group. A Phase IIIb, randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of dexmedetomidine for sedation during awake fiberoptic intubation. Am J Ther 2010;17:586-95.
19. Sturaitis M, Kroin J, Swamidoss C, Moric M. Effects of intraoperative dexmedetomidine infusion on hemodynamic stability during brain tumor resection. Anesthesiology 2002;98: A-310.
20. Bekker A, Basile J, Gold M, Riles T, Adelman M, Cuff G, et al. Dexmedetomidine for awake carotid endarterectomy: Efficacy, hemodynamic profile, and side effects. J Neurosurg Anesth 2004;16:126-35.
21. Tobias JD, Berkenbosh JW. Initial experience with dexmedetomidine in paediatric-aged patients. Paediatr Anaesth 2002; 12: 171-5.
22. Tobias JD, Berkenbosh JW, Russo P. Additional experience with dexmedetomidine in pediatric patients. South Med J 2003; 96: 871-5.
23. Tobias JD, Berkenbosh JW. Sedation during mechanical ventilation in infants and children: dexmedetomidine versus midazolam. South Med J 2004; 97: 451-5.
24. Bajwa SJ, Kaur J, Singh A, Parmar SS, Singh G, Kulshrestha A,et al. Attenuation of pressor response and dose sparing of opioids and anaesthetics with pre-operative dexmedetomidine. Indian Journal of Anaesthesia 2012;56: Issue 2.
25. Available from: http://www.ijaweb.org. Guo TZ, Buttermann AE, Jiang JY, Maze M. Dexmedetomidine injection into the locus ceruleus produces antinociception. Anesthesiology 1996;84:873-81.
26. Jaakola ML, Salonen M, Lehtinen R, Scheinin H. The analgesic action of dexmedetomidine - a novel α2-adrenoceptor agonist- in healthy volunteers. Pain 1991;46:281-5.
27. Tanskanen PE, Kytta JV, Randell TT, Aantaa RE. Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery. Br J Anesth 2006;97:658-65

28. Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY. Monitored Anesthesia Care with Dexmedetomidine: A Prospective, Randomized, Double-Blind, Multicenter Trial. Anesth Analg 2010;110:47-56.
29. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382-94.
30. Chrysostomou C, Di Filippo S, Manrique A, et al. Use of dexmedetomidine in children after cardiac and thoracic surgery. Pediatr Crit Care Med. 2006;7:126–
31. Chrysostomou C, Sanchez De Toledo J, Avolio T, et al. Dexmedetomidine use in a pediatric cardiac intensive care unit: can we use it in infants after cardiac surgery? Pediatr Crit Care Med. 2009;10:654–60.
32. Tokuhira N, Atagi K, Shimaoka H, et al. Dexmedetomidine sedation for pediatric post-Fontan procedure patients. Pediatr Crit Care Med. 2009;10:207–12.
33. Tobias JD, Berkenbosh JW, Russo P. Additional experience withdexmedetomidine in pediatric patients. South Med J 2003; 96: 871-5.
34. Gertler R, Brown HC, Mitchell DH, Silvius E. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent) 2001;14:13-21.