Original Article

Effect of Dexmedetomidine on Surgical Stress in Children Undergoing Elective Ophthalmic Surgery– A Prospective, Randomized, Comparative Study

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Abstract

Background: Surgical stress leads to neuro-endocrine response which causes metabolic derangements. Dexmedetomidine may attenuate stress response and pain in children undergoing ophthalmic surgeries.

Methods: Forty children between 8-14 years undergoing elective ophthalmic surgery were randomised into dexmedetomidine group (Group D) and saline group (Group C). After general anaesthesia, 0.5mcg/kg dexmedetomidine bolus and 0.5mcg/kg/hr infusion (Group D) or saline (Group C) was administered. Blood samples for serum cortisol and blood glucose were withdrawn a day before, 45 minutes after start of surgery and 1 hour after surgery. Intraoperative vitals, time for return of spontaneous respiration and airway device removal, emergence delirium, postoperative nausea and vomiting and pain were noted.

Results: Demographic data was comparable. Heart rate in the Group D was significantly lower from 5 to 25 minutes, at 50 and 60 minutes in comparison to the Group C. Serum cortisol, blood glucose and emergence delirium were comparable. The time to regain spontaneous respiration, SGA removal and to achieve MAS score of 9 was more in the Group D as compared to control group but it was not statistically significant. Postoperative pain scores were statistically lower in the Group D in comparison to the Group C at 10, 20, 60 and 120 minutes ($p<0.05$). Requirement of fentanyl boluses in PACU was significantly less in the Group D in comparison to the Group C (3 vs 11) ($p=0.008$).

Conclusion: Dexmedetomidine significantly reduces postoperative pain but does not have effect on serum cortisol and blood glucose in children undergoing elective ophthalmic surgery.

Keywords: Ophthalmic surgery, Dexmedetomidine, Cortisol, Glucose, Pain numeric scale

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Introduction

Stress response to surgery leads to metabolic and physiological derangements resulting in inflammatory, hormonal and genomic responses. Stress leads to increased level of serum cortisol due to failure of feedback mechanism of serum cortisol on Adrenocorticotrophic hormone (ACTH) and Corticotropin releasing hormone(CRH)which results in increased levels of blood glucose.[1] Increased cortisol and glucose level lead to adverse effects like immune suppression, cardiovascular and gastrointestinal complications. Intraoperative stress also leads to impaired operative outcome, impaired organ function, increased incidence of post-operative cognitive dysfunction and prolonged hospital stay.[2,3] In children, stress response may cause varied degree of pain, emergence delirium (ED), emergence agitation (EA) and metabolic complications.[1]

Stress response can be measured by surrogate markers like serum cortisol and blood glucose. The other stress response markers are glucagon, norepinephrine, epinephrine, insulin, interlukins (IL-1, IL-6), TNF- α, vasopressin. It has been observed that anxiolytics, fluid, glucose, adequate hydration and nutrition reduce undue catabolism. Fentanyl, Midazolam, Etomidate and Clonidine have been used successfully to reduce surgical stress response by providing adequate depth of anaesthesia, thus blunting the surgical response.

Dexmedetomidine is selective alpha 2 receptor agonist with sedative and anxiolytic properties.[4,5] It acts on locus ceruleus of brain stem and at spinal cord, which is responsible for providing analgesia and haemodynamic stability during surgery as well as procedural sedation.[6,7] It has opioid-sparing effect, does not cause respiratory depression and reduces EA, ED and post-operative nausea and vomiting (PONV).[8-12] Dexmedetomidine reduces intra ocular pressure (IOP) during ocular surgeries.[13,14] Dexmedetomidine is administered as 0.5 - 1 mcg/kg bolus over 10 minutes followed by 0.2 - 0.7 mcg/kg/hr infusion. Although opioids and benzodiazepines have been used to reduce surgical stress, Dexmedetomidine can be an effective alternative due to its unique properties.

Thus we evaluated the effect of Dexmedetomidine on the rise of serum cortisol and blood glucose levels peri-operatively in children undergoing elective ophthalmic surgeries under conventional general anaesthesia (GA).

Materials and Methods

After ethical committee approval, CTRI registration (CTRI/2016/01/006568) and informed parental/guardian consent, forty patients of ASA status I and II, aged 8-14 years, of either sex, scheduled for elective ophthalmic surgery under GA of more than 45 minutes duration were included. Patients were randomly divided into two groups of 20 each by computer generated random numbers. Children who had cardiac/hepatic/renal diseases, mental retardation, premedication with sedatives, surgical duration <45 minutes or whose

parent/guardian refused consent were excluded.

Pre-anaesthetic check-up was done a day prior to surgery and fasting instruction was written. Methodology, outcome and adverse effects were explained to parents and children. Blood samples were drawn for the baseline serum cortisol and blood glucose levels.

In the operation theatre, standard monitors (ECG, pulse oximetry, NIBP) were attached. Anaesthesia was induced with sevoflurane 8% in 100% oxygen at fresh gas flow of 5litre/min and intravenous cannula was inserted after achieving adequate depth of anaesthesia. Fentanyl 2 mcg/kg, Atracurium 0.5 mg/kg were administered and intermittent positive pressure ventilation was initiated for 3 minutes. Appropriate size supraglottic airway device (SGA) was inserted and secured.

Children in the group D received 0.5 mcg/kg Dexmedetomidine bolus over 10 minutes followed by 0.5 mcg/kg/hr infusion while children in the group C received normal saline at the same rates. Anaesthesiologist who was not involved in the study prepared Dexmedetomidine or normal saline in a 50 ml syringe. Anaesthesia was maintained with oxygen, air (FiO_2 0.5) and Sevoflurane (MAC 0.8 to 1.0). Ringer Lactate was administered intraoperatively accordingly to standard guidelines. Atracurium boluses were administered whenever required. Intraoperative vitals were monitored at baseline, intravenous cannula insertion, SGA insertion and at 5 minutes interval till the end of surgery.

If there was any increase in heart rate (HR) or mean arterial pressure (MAP) >20%, Fentanyl 0.5 mcg/kg was administered. If there was decrease in HR below 50/min, or oculocardiac reflex occurred, surgeon was asked to remove the stimulus and topical Proparacaine (0.5%) was administered. If HR remained<50/min, intravenous Atropine 20mcg/kg was administered. Intraoperatively blood samples were drawn again at 45 minutes after start of surgery and at 10 minutes before the end of surgery. At the end of surgery, Ondansetron 0.1mg/kg was administered and Dexmedetomidine infusion and Sevoflurane were stopped. At the start of spontaneous ventilation, Neostigmine 50mcg/kg with Glycopyrrolate 10mcg/kg was administered. Time taken from the switching off Sevoflurane to start of spontaneous breathing efforts was noted. Once the child had adequate spontaneous respiration, SGA were removed at MAC of 0.3.The time taken for SGA removal was also noted. Child was shifted to post anaesthesia care unit (PACU).

In PACU, EA (PAED score), PONV (PONV score), perioperative pain by Pain Numerical Rating (PNR) Scale was assessed. If PAED score was 7 to 9 (subsyndromal EA)then repeat observations were made at one hours, if the score were>10 then midazolam bolus 0.4 mg/ kg not exceeding 10 mg was administered. If PONV score was three, 0.1 mg/kg Ondansetron was repeated and in case of recurrent PONV Metoclopramide 150 mcg/kg was administered. Fentanyl 0.5 mcg/ kg was administered if PNR score was 4- 6.

In case PNR score was >6, Fentanyl 1 mcg/kg was administered. Post-operative sample were drawn one hour after surgery. The children were discharged from PACU once modified Aldrete score >9.

Statistical analysis

Mukhtar et al study[15] observed attenuation of the neuroendocrine response after administration of Dexmedetomidine in children undergoing cardiac surgery. Blood glucose was 180 + 35 mg% in control group and 145 + 25mg% in Dexmedetomidine group after cardiopulmonary bypass. This calculation established that we required 16 patients in each group with a power of 90% and alpha error of 5%. We enrolled 20 children in each group considering dropout during study. Statistical analyses were performed using STATA14 software. The results are expressed as the mean + SD or percentage. A p value of <0.05 was considered to be statistically significant. Statistically appropriate tests were applied to the data.

Results

A total 40 patients were randomized in the present study. (Figure 1) Age, weight, duration of surgery, type of surgery and type of SGA were comparable in both the groups.

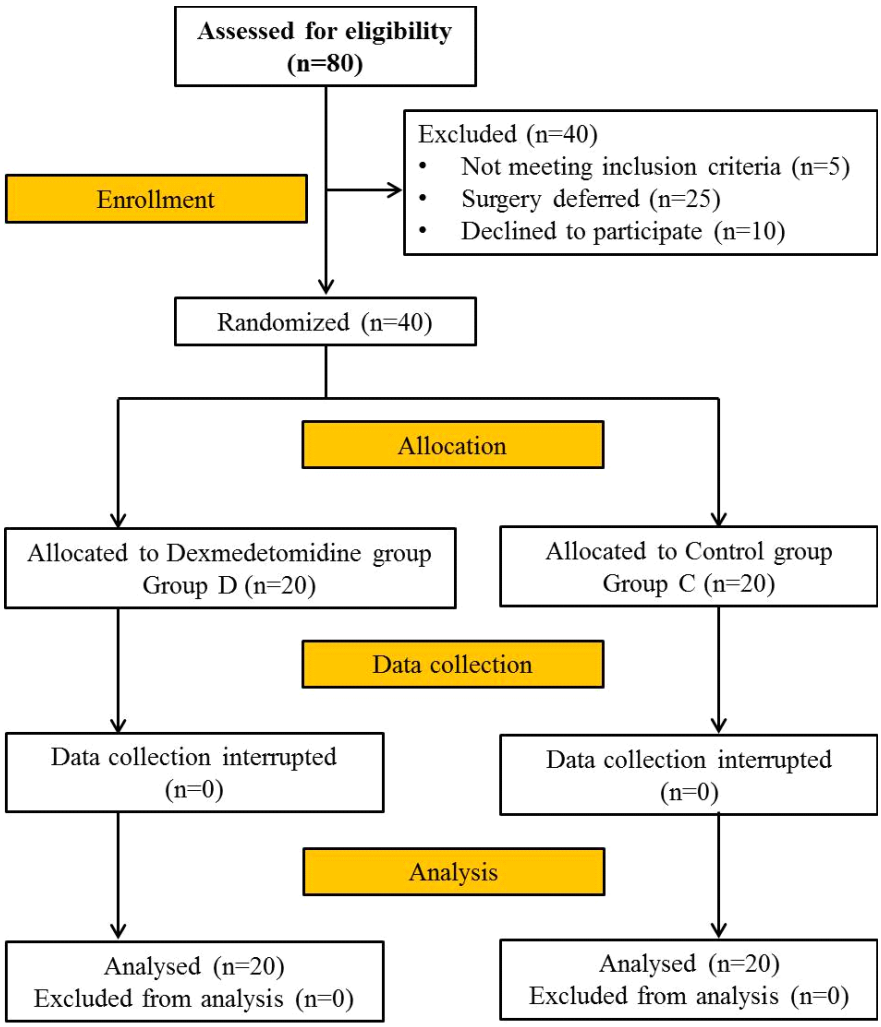


Figure 1: Consort Diagram

Male patients were more in the Group D in comparison to the Group C (p = 0.04). (Table 1)

Table 1: Demographic data of the Group D and Group C

Variable		Group D n=20	Group C n=20	p value
Age, years		11 ± 2.36	11.2 ± 1.98	0.77
Weight, Kg		33(22-45)	38.5(18-58)	0.28
Sex, n (%)	Male	17 (85)	10 (50)	**0.04***
	Female	3 (15)	10 (50)	
Duration of surgery, minutes		82.5 (50-120)	65 (50-120)	0.07
Indications for surgery, n (%)	Corneal surgery	5 (25)	2 (10)	0.15
	Lid surgery	0 (0)	1 (5)	
	Vitrectomy	3 (15)	7 (35)	
	Vitro – retinal	12 (60)	8 (40)	
	Glaucoma surgery	0 (0)	2 (10)	
Type of Supra Glottic Airways, n (%)	Ambu Laryngeal Mask	4 (20)	4 (20)	0.74
	Flexible Laryngeal Mask Airway	6 (30)	4 (20)	
	Air Q Intubating Laryngeal Airway	10 (50)	12 (60)	

Data are presented as mean ± standard deviation or median [Range] or absolute numbers (with the percentage of the whole) *p < 0.05 statistically significant

The blood glucose level and serum cortisol level at the pre-operative, intra-operative and post-operative period were comparable between the two groups. (Table 2)

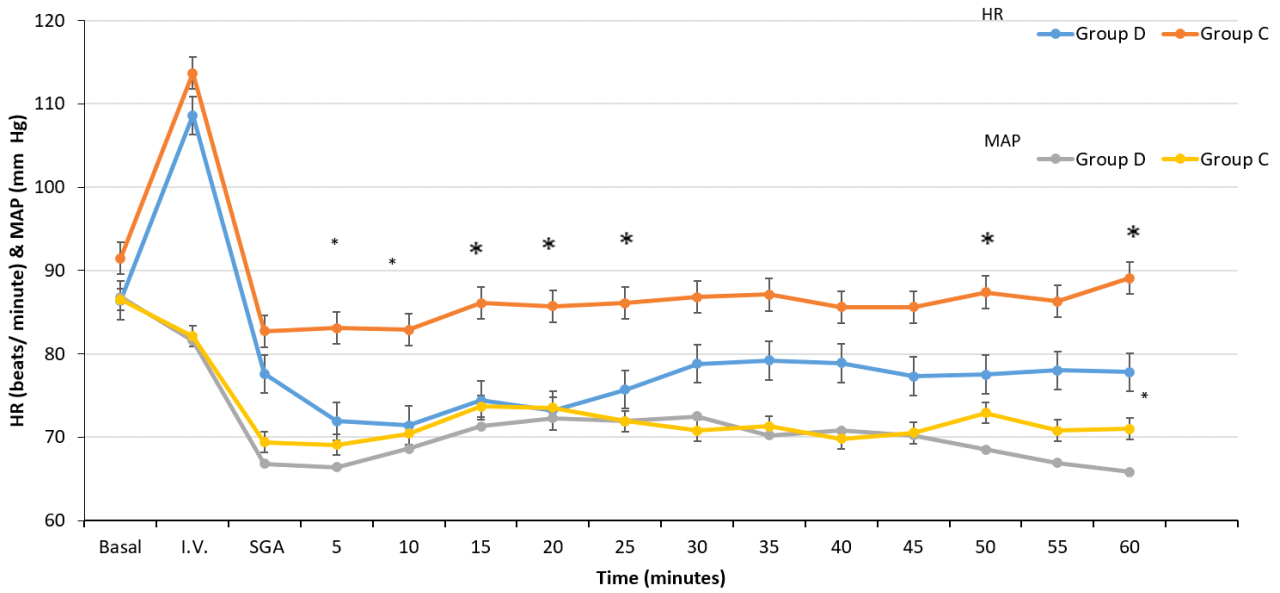
Table 2: Blood glucose and Serum cortisol levels at different time intervals in both the groups

		Group D, n=20	Group C, n=20	p value
Serum glucose (mg/dl)	**Pre-operative**	87.5 (75-122)	84 (58-115)	0.36
	Intra-operative	98 (71-117)	85.5(72-110)	0.08
	Post-operative	89 (64-117)	92(68-130)	0.22
Serum cortisol (mcg/dl)	**Pre-operative**	3.83 (1.52-13.07)	2.52(0.8-15.32)	0.14
	Intra-operative	7.19 (0.21-20.59)	4.55(0.56-17.67)	0.16
	Post-operative	11.66 (1.39-24.85)	12.92(0.78-23.9)	0.82

Data are presented as median (Range), n=number of patients, *p < 0.05 statistically significant

In Group D, HR was significant lower from 5 to 25 minutes and at 50 and 60 minutes in comparison to the Group C. In the Group D, MAP was lower at 60 minutes in comparison to the Group C. (Figure 2)

Figure 2. Heart rate (HR) & Mean arterial Pressure (MAP) at different time points



The time to regain spontaneous respiration after switching off the Sevoflurane, time for SGA removal was more in the Group D as compared to control group but it was not statistically significant. PNRS scores were statistically lower in the Group D in comparison to the Group C at 10 minutes, 20 minutes, 60 minutes and 120 minutes. (Table 3)

Table 3: Supraglottic airway removal time (SGAR), Time to regain spontaneous respiration (TS) and Pain Numeric Rating Scale (PNR)

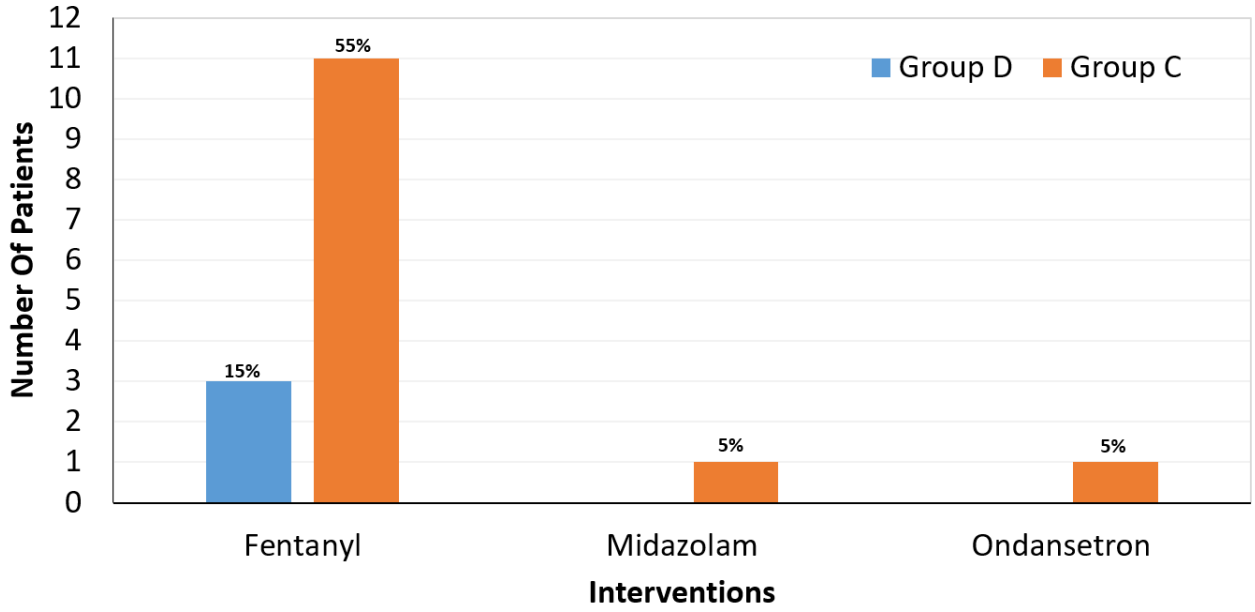
Parameters		**Group D, n=20**	**Group C, n=20**	**p value**
SGA removal time (minutes)		6.15 ± 1.79	5.17 ± 1.29	0.05
Time to regain spontaneous respiration (minutes)		3.92 ± 1.60	3.01 ± 1.36	0.06
PNR score	0 minutes	0 (0-3)	0 (0-6)	0.08
	10 minutes	0 (0-3)	0 (0-5)	**0.03***
	20 minutes	0 (0-4)	2 (0-6)	**0.0003***
	60 minutes	1.5 (0-4)	3 (0-6)	**0.001***
	120 minutes	2 (0-3)	3 (2-4)	**0.01***
	240 minutes	2 (1-3)	3 (1-4)	0.21

Data are presented as mean+ SD; median [Range] , n=number of patients, *p < 0.05 statistically significant

Time to achieve MAS median score of 9 was more in the Group D as compared to control group but it was not statistically significant.

Requirement of fentanyl boluses in PACU was significantly less in the Group D in comparison to the Group C (3 vs 11) (p=0.008). In the Group C, one child received Midazolam and another child received Ondansetron. (Figure 3)

Figure 3. Postoperative interventions in both the groups



Discussion

In the present study, Dexmedetomidine infusion did not decrease serum cortisol and blood glucose level in children undergoing elective ophthalmic surgeries.

Our results are contradictory to the published studies which showed dose dependent reduction in stress response in terms of serum cortisol, blood glucose levels and norepinephrine concentration with Dexmedetomidine.[16] There are many factors which can lead to change in serum cortisol level like physical activity, anorexia nervosa, alcoholism, hypo/hyperestrogenism and drugs like anticonvulsants, contraceptive pills, steroid etc. Preoperative condition of the patient like sepsis, hypermetabolic state, pain, drugs intake also affects the serum cortisol and blood glucose levels. Dexmedetomidine effect on stress response has been mainly studied in cardiac, neuro and abdominal surgeries. Difference in severity of stress response with different surgeries and intraoperative hypothermia, supratentorial tumor surgery, pneumoperitoneum may affect on change in serum cortisol and blood glucose level Dexmedetomidine has been used at variable dosage and routes in different studies including single bolus at the start or at the end of surgery, bolus followed by infusion, only infusion at different doses.[17,18,19,20]Variable anaesthetic techniques like use of nitrous oxide, laryngoscopy, inadequate pain relief affect the stress response.

We tried to reduce factors influencing the cortisol level by including ASA 1 and 2 children and by excluding patients who were receiving anticonvulsant, steroid. We included both male and female children as serum cortisol is not affected by the gender difference in children.[21] We used SGA for airway management to avoid laryngoscopy response and its contribution to stress.[22] Present study is done in ophthalmic surgeries which result in minimal haemodynamic variation and is less painful in comparison to cardiac and abdominal surgeries. We administered 2mcg/kg fentanyl for adequate analgesia in both the groups. The difference in preoperative condition, the type and duration of surgery, haemodynamic variation and pain stimulus might be attributed to difference in adequate stress control in the control group. In the present study, Dexmedetomidine resulted in significant reduction in the postoperative pain scores in comparison to the control group till 120 minutes. Three patients required fentanyl in the group D in comparison to 11 patients in the group C. ($p = 0.008$) Other studies have also shown reduction in fentanyl requirement postoperative with Dexmedetomidine.[18] Dexmedetomidine has analgesic property because of its effect on presynaptic α_2 receptors which inhibits release of norepinephrine, terminating the propagation of pain signals.[23] In the present study, HR and MAP were significantly lower in the Dexmedetomidine group ($p < 0.05$) as compared to the control group at various time points, but it didn't cause haemodynamic instability and didn't require any intervention. Decrease in HR and MAP with Dexmedetomidine has been observed in several studies due to its action on central as well as peripheral presynaptic α_2 receptors leading to decreased sympathetic tone.[24]

In the present study, the time to regain spontaneous respiration, SGA removal and time to achieve MAS score of 9 was more in the Dexmedetomidine group as compared to control group. Though this difference was not statistically significant, 10 minutes difference in each case may be clinically significant in a busy theatre. Sedative effects of Dexmedetomidine and continuation of infusion till the end of surgery could be contributing factors for the increased time.[24]The use of BIS/entropy to titrate the inhalational agent may affect the timings to regain spontaneous respiration and SGA removal.[25]

In the present study, PAED, PONV score were comparable in both the groups. Previous studies showed reduction of ED and EA with Dexmedetomidine, shorter duration of surgeries might be the reason for this difference.[18,26,27,28] We administered Ondansetron in both the groups due to high incidence of PONV in the ophthalmic surgeries.

Limitations of the present study include short duration of surgery and subjective measurement of depth of anaesthesia to titrate inhalational agentwhich would have affected the EA, ED and recovery time.

To conclude, Dexmedetomidine bolus followed by infusion did not decrease serum cortisol and blood glucose level in children between eight to fourteen years for elective ophthalmic surgery of 45 minutes to 120 minutes duration, however it significantly reduced postoperative pain and fentanyl requirement.

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Conflicts of interest

There are no conflicts of interest

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