CONTINUOUS INFUSION OF DEXMEDETOMIDINE TO ATTENUATE THE HEMODYNAMIC RESPONSE DURING LAPAROSCOPIC SURGERY IN CHILDREN

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ABSTRACT

BACKGROUND

Video laparoscopic surgeries have become popular in paediatric age group. However, the stress response to laparoscopic surgeries is high due to sympathetic stimulation and increased secretion of pituitary hormones. Dexmedetomidine is highly specific, potent, selective α2 agonist which obtunds the hemodynamic stress response during laparoscopic surgeries by decreasing HR and MAP with concomitant decrease in cortisol, catecholamine and sympatholytic action also.

Aims and Objectives- To evaluate the hemodynamic stress response to nociceptive stimuli in children submitted to video laparoscopic surgeries under balanced anaesthesia and IV Dexmedetomidine.

MATERIALS AND METHODS

This non-randomized, control trial study involving 30 ASA I and II children (1-12 years) posted for elective laparoscopic surgeries. Patients were assigned to 2 groups- Group D (Dexmedetomidine) and Group C (Control). All children were pre-medicated with oral midazolam 0.5 mg/kg. Basal HR, BP and SpO2 were recorded in all groups. Induced with Sevo + O_2 + Air. Group D received bolus infusion of Dexmedetomidine 1 mg/kg over 10 minutes followed by 1 mg/kg infusion as maintenance whereas Group C received normal saline infusion at similar rate and volume. During different surgical anaesthetic periods HR, SBP, DBP, $ETCO_2$, SpO_2, InISO, EtISO and duration of surgeries were compared in both the groups. Need of supplemental Fentanyl was noted.

RESULTS

During the strongest nociceptive stimuli like laryngoscopy and abdominal port placement, the heart rate and systolic blood pressure increased significantly in Group C compared to Group D (At M_3 P-Value 0.008 and at M_4 0.037). The need for supplemental fentanyl and hemodynamic parameters were similar in both the groups. The sample size was taken for conveniences.

CONCLUSION

Continuous infusion of Dexmedetomidine as an adjuvant to inhaled isoflurane combined with isoflurane anaesthesia effectively attenuates the hemodynamic responses to noxious stimuli at various stages of the laparoscopic surgeries in children.

KEY WORDS

Paediatric Laparoscopy, Dexmedetomidine in Laparoscopy.

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BACKGROUND

Currently, video laparoscopy has become more popular and widespread for many surgeries in children. Technical advances in miniaturing the instruments and opticals and increased experience with laparoscopy have allowed these surgical techniques to be increasingly used in Paediatric patients.[1] Dexmedetomidine has been investigated in pediatric patient, now there is an evidence to support the use of this drug as sedative and anaesthetic adjuvant in children. It has minimal respiratory depression action and modest cardiovascular effects it is used to obtund the stress response during surgical process.[2]

The stress response to surgery is characterised by increased secretion of pituitary hormones and activation of the sympathetic nervous system.[3] Attenuation of this stress response may improve outcome of organ functions and post-operative recovery. Unlike other sedatives Dexmedetomidine is also used in MRI because of its less respiratory depression action.[4] So, it is commonly used for sedation outside the OR like MRI. Balanced anaesthesia with inhaled agents in combination with different opioids has been the method for these procedures.[5] However, there is a scope for tailor-made anaesthesia techniques to obtund the cardiovascular response to noxious stimuli during the laparoscopic surgery.

Dexmedetomidine is a selective and potent α2 Adreno-receptor agonist with hypnotic, analgesic and sympatholytic properties. It reduces sympathetic responses to nociceptive stimuli reduces the usage of other anaesthetics and improves the intra-op hemodynamic stability.[1] Dexmedetomidine produces sedative state in number of ways and is dose dependent. At low doses it produces only sedation but arousable and cooperative. In large doses it produces deep sedation or even general anaesthesia.[2]

This non-randomized, control trial study aimed to assess hemodynamic responses to nociceptive stimuli, when Dexmedetomidine is used as an adjuvant anaesthetic to isoflurane in paediatric patients undergoing video laparoscopic surgeries. The need of supplemental fentanyl doses to maintain hemodynamic parameters stable during surgery was also evaluated.

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MATERIALS AND METHODS

Between 2010 and 2011. This non-randomized, control trail study was conducted in 30 children of IGICH Bangalore (1 to 12 years) submitted to video laparoscopic surgeries. The sample size taken for conveniences.

- Decision for the surgical approach (Laparotomy or video laparoscopic) was taken by the surgeon with no interference from the researchers.
- Only ASA grade I and II were included in the study
- The study protocol was submitted to and approved by Research Ethics committee of hospital (IGICH)
- Parents or legal surrogates were informed, and consents were taken from them.
- Children with a history of allergy to midazolam, fentanyl, propofol, atracurium, isoflurane and Dexmedetomidine were excluded from the study.

On admission to the surgical ward, patients were assigned to the following groups:

1. Group D (Dexmedetomidine) - Dexmedetomidine was infused (1 mg/kg) as bolus for 10 minutes followed by maintenance infusion (1 mg/kg) until the end of the surgery.
2. Group C (Control) - Normal saline solution infusion at the same rate and volume used for Dexmedetomidine administration as adjuvant for ISO.

All children fasted a period of at least 6 hours with pre-operative-antibiotic coverage as prescribed by surgeons.

Stages of Anaesthesia

1. **Pre-Anaesthetic Medication:** All children received oral midazolam 0.5 mg/kg in pre-op holding area and vitals were monitored like HR, BP and SpO_2.
2. **Anaesthesia Monitoring:** Continuous ECG (Lead II), NIBP, and SPO_2 were monitored. InISO and EtISO were also monitored.
3. **Induction and Maintenance of Anaesthesia:** Anaesthesia was performed after 10 minutes of IV administration Dexmedetomidine (bolus). Concurrently sevoflurane 1% was inhaled in order to blind the surgical team to the induction agent. After 10 minutes IV Thiopentone 5 mg/kg was infused and trachea was intubated after 3 minutes of injecting atracurium. Maintenance of anaesthesia was with Isoflurane 1% Fentanyl + O_2 + Air. If the systolic blood pressure and HR increases more than 20% of the basal line, managed with fentanyl top up dose or and increment in the dial settings of isoflurane was done. For adequate surgical relaxation atracurium infusion of 0.5 mg/kg/hour was started.
4. **Intra-Operative Maintenance:** hemodynamic parameters were pre-defined to prevent hypotension and decreasing cardiac output as well as to provide adequate analgesia-
    1. When systolic Blood Pressure is dropped & was greater than 20% of base line, isoflurane concentration was reduced by 1% to 0.5% with concomitant use of ringer lactate (RL) infusion. If systolic blood pressure was still low Dexmedetomidine infusion was reduced by 50%. If the systolic blood pressure continued to remain low, Dexmedetomidine infusion was stopped and the patient was excluded from the study.
    2. When Systolic Blood Pressure increased more than 20% from base line, fentanyl 1 µg/kg was administered.
    3. When the HR is decreased more than 20% from the base line, a dose of 0.01 mg/kg IV atropine was administered.

Data were collected using a standardized protocol which included demographic data, fluid infusion, infused drugs, length of the surgery and ISO volume administered.

The SBP, DBP and HR SpO2 EtCO2 were defined as major parameters to assess the hemodynamic response to nociceptive stimuli during the following periods.

Baseline M0 – after premedication and prior to induction

M_1 – after induction before intubation

M_2 - after Dexmedetomidine infusion

M_3 – after intubation (immediately after intubation)

M_4 – first port insertion.

M_5 – maximum CO2 insufflation

M_6 - Second port insertion

M_7 - III port insertion

Maintained on air + O2 + Isoflurane 0.5% and during maintenance dial settings will be adjusted according to hemodynamic changes.

All unexpected events during anaesthetic induction and surgery time were recorded. Adverse effects as well as the need for the supplemental doses of fentanyl for maintenance of intra-operative hemodynamic parameters were noted.

Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t-test has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

RESULTS

Between 2010 and 2011, 30 children were subjected to laparoscopic surgeries in Indira Gandhi Institute of Child Health. The demographic data showed that both groups were homogenous in terms of age, weight, gender and baseline hemodynamic parameters. Results regarding SBP, DBP and HR at different moments of analysis are shown in the line graphs and are as follows.

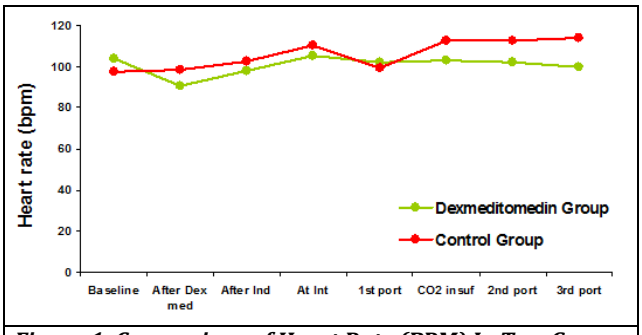

Figure 1. Comparison of Heart Rate (BPM) In Two Groups of Patients Studied

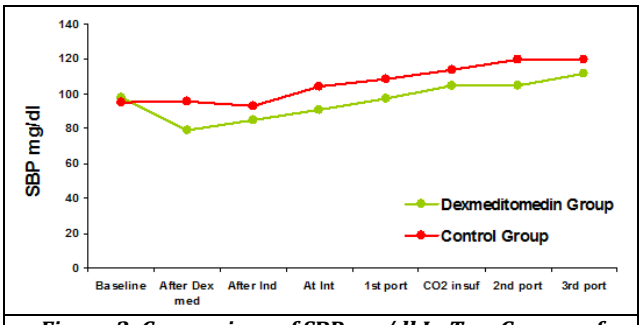

Figure 2. Comparison of SBP mg/dl In Two Groups of Patients Studied

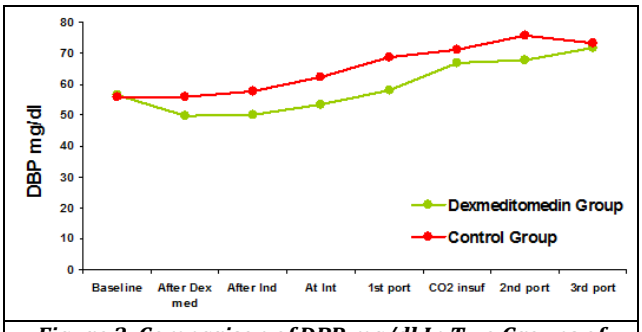

Figure 3. Comparison of DBP mg/dl In Two Groups of Patients Studied

Systolic Blood Pressure

- As seen in Figure 2 there was a remarkable increase in the systolic blood pressure in the control group when compared to Dexmedetomidine group.
- M_1 – (0.008), M_2 - (0.83), M_3 - (0.0005) and the mean values at these points are higher in Group C than in Group D. Increase in SBP at M_6 was not significant.

Diastolic Blood Pressure

- As observed in Figure 3 there was a slight increase in DBP in control group (0.089) at M1 & (0.062) at M3.
- There were no changes in diastolic blood pressure in both the groups during assessment and statically also.

Heart Rate

- As seen in Figure 1 there was an increase in heart rate in control group when compared with the Dexmedetomidine group at M2, M4, M5, and M6. However, it was statistically not significant.
- One patient in Dexmedetomidine group at the end of the infusion bolus showed bradycardia i.e., more than 30% of Basal HR and treated with atropine.

Characteristics	Group D	Group C	P value
Age (in years)	5.67 ± 2.26	7.00 ± 3.57	0.245
Weight (in kg)	17.71 ± 5.54	18.61 ± 7.39	0.713
Gender	5/10	5/10	1.000
SBP M_0	97.85 ± 17.23	94.87 ± 11.24	0.582
DBP M_0	56.57 ± 10.92	55.80 ± 9.79	0.843
HR M_0	104.14 ± 20.42	97.33 ± 16.33	0.329
Duration of Surgery	1.69 ± 0.61	1.91 ± 0.92	0.473
Premed	15	15	1.000
Et CO_2	23.71 ± 4.68	23.83 ± 5.4	0.900

Table 1. General Characteristics of The Participants

		Group D	Group C	P value
Base Line Values	SBP	97.85 ± 17.23	94.57 ± 11.24	0.002
	DBP	56.57 ± 10.92	55.80 ± 9.79	0.014
	HR	104.14 ± 20.42	97.33 ± 16.33	0.016
After Dex	SBP	78.85 ± 21.60	95.53 ± 6.50	0.001
	DBP	49.92 ± 9.22	55.87 ± 8.90	0.004
	HR	90.64 ± 16.04	98.53 ± 17.12	0.022
After Induction	SBP	84.71 ± 7.45	92.8 ± 15.15	0.008
	DBP	50.07 ± 10.20	62.20 ± 14.23	0.089
	HR	97.71 ± 17.37	102.27 ± 16.61	0.212
After Intubation	SBP	90.64 ± 8.84	104.13 ± 13.93	0.005
	DBP	53.50 ± 8.99	62.20 ± 14.23	0.062
	HR	105.57 ± 16.95	110.27 ± 16.61	0.458
1st Port	SBP	97.14 ± 11.98	108.47 ± 15.39	0.037
	DBP	58.14 ± 11.81	68.73 ± 14.66	0.042
	HR	102.14 ± 21.90	99.33 ± 29.27	0.773
CO_2 Insufflation	SBP	104.65 ± 16.55	108.47 ± 15.39	0.001
	DBP	66.78 ± 17.26	68.73 ± 14.66	0.016
	HR	102.93 ± 23.36	99.33 ± 29.27	0.022
2nd Port	SBP	104.50± 13.69	119.93 ± 11.42	0.002
	DBP	67.85 ± 14.83	75.60 ± 13.07	0.014
	HR	102.27 ± 16.833	112.67 ±	0.010

Table 2. Hemodynamic Parameters Recorded During Different Surgical Moments.

DISCUSSION

In this clinical study in which Dexmedetomidine was compared to normal saline as an adjuvant anaesthetic to inhalational agent Isoflurane in children submitted to video laparoscopic surgeries.

The following observations were made

1. The hemodynamic changes to the nociceptive stimulus were higher in control group as compared with Dexmedetomidine group.
2. These are mainly due to changes in hear rate sec to nociceptive stimulation.
3. There was a significant change or increase in the systolic pressure in control group when compared to Dexmedetomidine group.
4. Supplemental dose of Fentanyl for maintaining the hemodynamic parameters stable during surgeries were not comparable between the two groups.

Dexmedetomidine is a known sedative, analgesic and sympatholytic action. Dexmedetomidine causes sympatholytic action combined with increase in the vagal activation and causes lower increase of blood pressure level and the heart rate when compared to placebo.[1]

Dexmedetomidine reduces the norepinephrine/ catecholamine level by 50% & they remain low even in the presence of nociceptive stimuli also.[6]

Dexmedetomidine is highly specific, potent and selective α2 agonist, has relatively high ratio of α2/α1 activity (1620;1 as compared to 220;1 for clonidine) and therefore, it is considered as full agonist.[3] This ratio ensures its potent action on CNS without unwanted CVS effects from α1 receptor activation.

Ahmed M et al., had a randomised placebo control study in 30 paediatric patients undergoing open heart surgeries were assigned to two equal groups and reported the sympatholytic effects of a continuous intra-operative infusion of Dexmedetomidine on CVS and stress hormones (Cortisol and chatecholamines).[3] This is the first study to report the sympatholytic effects of continuous infusion of Dexmedetomidine on CVS and stress hormones in paediatric patients.

Dexmedetomidine when used as a sole agent with the guidelines of the FDA does not provide consistent success for radiological imaging.[3] Mason et al trialled Dexmedetomidine sedation with higher doses of both bolus (2 micrograms /kg) and infusion (1 microgram /kg /hour) and was successful in sedation for 60 children for CT scans.[4]

Some studies have shown remarkable increase in MAC of iso, decrease in consumption of when combined with continuous infusion of Dexmedetomidine at plasma concentration of 0.3 - 0.6/ml.[7]

Suppression of hemodynamic response to nociceptive stimuli with -concomitant reduction in hormone release is one of the major goals of adequate anaesthesia.[8] Studies addressing the use of Dexmedetomidine in children are less, most publications are case reports showing the intra-operative use of Dex.[8]

Blood pressure and HR are the hemodynamic variables used to assess the adequate block of the response to surgical stimulation.[9,10]

Limitation of this study is that we have not used BIS to monitor the depth of anaesthesia. To correlate with the control of hemodynamic changes caused by nociceptive stimuli.[11]

There was no change in the diastolic blood pressure between the groups. This effect is attributed the high peripheral vascular resistance caused by catecholamine release in the response to the nociceptive stimuli would be blocked with the effect of Dexmedetomidine infusion.[12]

Clinical trials are done with Dexmedetomidine in children are restricted to sedation for MRI and as pre-anaesthetic to reduce the agitation caused by Sevoflurane. [13,14]

It should be highlighted that inadequate analgesic is not the only factor interfering with the hemodynamic changes during laparoscopy. The increase in intra-abdominal pressure and CO_2 insufflation increases the peripheral vascular resistance and decreases the stroke volume.[15,16,17]

Systolic blood pressure unlike the heart rate remains stable in control group during intubation and umbilical port may be due to hypotensive effect of thiopentone used for induction.[1] Difference in response was due to sensitivity of the patient to the drug.

The current study showed that an initial dose of Dexmedetomidine 1 mg/kg followed by maintenance dose of 1 mg/kg as an adjuvant to isoflurane in children who underwent video laparoscopic surgeries, kept the systolic blood pressure, diastolic blood pressure and heart rate stable also at the time of surgical and nociceptive stimulation.

Maria C.S et al, also worked upon this type of study where Dexmedetomidine combined with isoflurane for anaesthesia of children submitted to video laparoscopic appendicectomy efficiently blocks the hemodynamic responses to nociceptive stimuli. ($p<0.001$) It did not change the need for supplemental doses of fentanyl for the hemodynamic maintenance during intra-operative period.[1]

CONCLUSION

Continuous infusion of Dexmedetomidine as adjuvant with isoflurane effectively attenuates the hemodynamic response to nociceptive stimuli like intubation, trocar insertion, and CO_2 insufflation in paediatric patients undergoing laparoscopic surgeries.

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