Original Research Article

A Hospital Based Prospective Randomized Double Blinded Comparative Study of Two Different Doses of Dexmedetomidine Infusion on Haemodynamic Stress Response

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Abstract

Background: Balanced anaesthesia protocols include combination of drugs of different classes used with specific purpose to create unconsciousness, muscle relaxation, analgesia and amnesia. Dexmedetomidine is a high selective centrally acting, potent alpha2 adrenergic agonist with short duration of action. The primary objective of this study was to compare the efficacy of two doses of Dexmedetomidine (0.2 and 0.4 µg/kg) as a 15 min infusion before induction for attenuating the hemodynamic stress response. **Materials & Methods:** This is a prospective, randomized, double blinded clinical study done on 40 patients between 18 and 55 years of age belonging to American Society of Anaesthesiology physical status 1 and 2 of either sex undergoing a variety of elective laproscopic surgeries under general anaesthesia in Government Medical College, Dungarpur, Rajasthan, during six month of period. The patients were randomly allocated into two groups of 20 patients each, Group Dex 0.2 (patients receiving Dexmeditomidine infusion 0.2 mcg/kg/h) and Group Dex 0.4 (patients receiving Dexmedetomidine infusion 0.4 mcg/kg/h). All the patients were observed for vital parameters like PR, MAP and SpO_2 at regular intervals including before starting the infusion, 15 min after starting the infusion, after induction, after intubation, after creation and release of pneumoperitoneum and after extubation. **Results:** The results were statistically better in Dex 0.4 group compared with Dex 0.2 group. Post-operative 24 hour analgesic requirements were much less in both the groups (better effect in Dex 0.4 group). No significant side effects were noted. **Conclusion:** Low dose Dexmedetomidine infusion in the dose of 0.4 mcg/kg/h effectively attenuates haemodynamic stress response during laparoscopic surgery with reduction in post-operative analgesic requirements.

Keywords: Infusion, Dexmedetomidine, MAP, PR, Stress Response.

Introduction

Modern anaesthesia practice plan to prevent sympathetic discharge and provide haemodynamic stability perioperatively. Various variety of agent like opioid analgesics, benzodiazepines, beta blockers, calcium channel blockers and vasodilators have been used to achieve this objective with variable success. In last few years, a great enthusiasm has been shown towards the use of α2 agonists in anaesthesia practice because of their anxiolytic, sedative, sympatholytic and analgesic sparing properties[1].

Balanced anaesthesia protocols include combination of drugs of different classes used to create unconsciousness, muscle relaxation, analgesia and amnesia. As the drugs are used in low to moderate doses, the adverse effects are reduced. So anaesthesia induction, maintenance and emergence are safer, smoother and comfortable. Maintenance of heart rate, blood pressure and depth of anaesthesia are important in the intra-operative period. Laryngoscopy and intubation can lead to hemodynamic stress response which can be controlled by suitable agents various drugs like lignocaine, nifedipine, Beta blockers, nitro glycerine etc. are used to reduce hemodynamic stress response to laryngoscopy and intubation[2].

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Dexmedetomidine is a high selective centrally acting, potent alpha2 adrenergic agonist with short duration of action. Alpha 2 to alpha 1 selectivity for Dexmedetomidine is 1620:1 compared to 220:1 for clonidine. Dexmedetomidine has sedative, anxiolytic, analgesic and sympatholytic properties[3].

Various studies have been done using intravenous Dexmedetomidine for analgesia, anxiolysis and sedation during surgery. The primary objective of this study was to compare the efficacy of two doses of Dexmedetomidine (0.2 and 0.4 µg/kg) as a 15 min infusion before induction in attenuating the hemodynamic stress response.

Materials & methods

This is a prospective, randomized, double blinded clinical study done on 40 patients between 18 and 55 years of age belonging to American Society of Anaesthesiology physical status 1 and 2 of either sex undergoing a variety of elective laproscopic surgeries under general anaesthesia in Government Medical College, Dungarpur, Rajasthan, India during six month of period.

Inclusion Criteria

1. Patients giving valid consent.
2. Patients under American Society of Anaesthesiology physical status 1 and 2.
3. Patients undergoing elective laproscopic surgeries under general anaesthesia.
4. Patients aged between 18 to 55 years.

Exclusion Criteria

1. Refusal by the patient.
2. Patients with American Society of Anaesthesiolog y physical status 3 or more.
3. Patients posted for emergency surgeries.

4. Patients with history of alcohol or drug abuse.
5. Patients who are allergic to any of the test drugs.
6. Contraindication to general anaesthesia.

Pre-operative Check-up

A thorough pre-anaesthetic check-up was carried out. Detailed history was taken and systems were examined. Pulse, blood pressure and respiratory rate were noted. Height and weight were recorded. Routine investigations like haemogram, bleeding time, clotting time, blood sugar, Renal function test, liver function test, chest X-ray and ECG were obtained before taking up for surgery. Inclusion and exclusion criteria were applied.

Pre-operative Preparation

All the selected patients were examined on the day prior to surgery, explained in detail about the anaesthetic procedure and informed written consent was obtained. All patients were kept NPO 6 hours prior to surgery. They received Tablet Ranitidine 150mg and Tablet metoclopramide 10mg. on the previous night and on the morning of surgery.

Intra-operative monitoring included- Pulse rate, oxygen saturation, noninvasive blood pressure, ECG, Capnography.

Preparation of drug for infusion

Infusion was prepared according to the group allotted in a separate O.T. To prepare the infusion, Dexmedetomidine 0.5 ml containing 50 µg of the drug was withdrawn in a 20 ml. syringe and was diluted up to 12.5 ml with normal saline resulting in the final concentration of 4 mcg/ml, while for other group, Dexmedetomidine 0.25 ml containing 25 µg of the drug was withdrawn in a 20 ml. syringe and was diluted up to 12.5 ml resulting in the final concentration of 2 mcg/ml. Dexmedetomidine infusion of group appropriate concentration was given through infusion pump, depending on the weight of the patient.

The patients were randomly allocated by envelope method into two groups of 20 patients each, Group Dex 0.2 (patients receiving Dexmeditomidine infusion 0.2 mcg/kg/h) and Group Dex 0.4 (patients receiving Dexmedetomidine infusion 0.4 mcg/kg/h).

For blinding of the study, syringes were prepared by other anesthetist, outside OT, and handed over to assessor, with instruction of rate of infusion at the start of study. Thus, the assessor and the patient did not come to know about the grouping of the patient and only the rate of injection was different according to the weight and group of patient. Decoding of blinding to the assessor was done only at the time of tabulation and result analysis.

After taking the patient on the operation table, a multipara monitor was attached and the baseline pulse rate (PR), mean arterial pressure (MAP) and oxygen saturation were noted down. A wide bore intravenous cannula was inserted for giving the intravenous fluids, and another line was taken up for the infusion pump. Premedication was administered 30 minute before induction of anaesthesia to all the patients in the form of injection glycopyrrolate .2mg iv and injection tramadol 100mg iv and inj ondansetron 4mg iv as per the institutional protocol.

After 15 minute, drug infusion stopped and pre-oxygenation was performed. Patients were induced with injection propofol 2 mg/kg intravenously followed by injection succinyl choline 1.5 mg/kg intravenously. Laryngoscopy and endotracheal intubation performed with appropriate size cuffed endotracheal tube. Anaesthesia was maintained with O_2:N_2O (50:50), isoflurane and injection vecuronium bromide as a muscle relaxant. Intra-abdominal pressure was maintained between 12 and 14 mmHg throughout the laparoscopic procedure. The patients were mechanically ventilated using circle system to keep the $EtCO_2$ between 30 and 40 mm Hg. Anaesthetic agents were stopped at the end of surgery. Reversal was carried out with inj neostigmine 2.5mg and inj glycopyrolate 0.4mg followed by extubation by conventional methods.

All the patients were observed for vital parameters like PR, MAP and SpO_2 at regular intervals including (before starting the infusion, 15 min after starting the infusion, after induction, after intubation, after creation and release of pneumoperitoneum and after extubation). Patients were also observed for time required for extubation, post-operative sedation level, time to first rescue analgesic requirement post- operatively, when pain reported by patient was ≥ 4 on visual analogue scale [VAS], total amount of analgesic drug required during the first 24 h post-operatively and the adverse effects. Injection diclofenac sodium 1.5 mg/kg IM was used as rescue analgesic and thereafter whenever the VAS score became ≥4.

Statistical methods of analysis

All parameters to be entered in Microsoft excel spread sheet and statistically analysed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Statistical analysis of demographic data, heart rate changes, blood pressure changes were done by unpaired 't' test. Student's t test was used for comparing means of two populations.

Results

In the study, both groups were comparable to each other with respect to age, sex, weight, ASA grading, duration of surgery and anaesthesia [Table 1].

Table 1: Demographic characteristics and duration of surgery and anaesthesia

Variables	Group Dex 0.2%	Group Dex 0.4%	P-value
Age (yrs)	41.37±7.84	42.12±7.76	>0.05
Sex			
Male	7	6	>0.05
Female	13	14	
Weight (kg)	54.96±7.36	53.78±6.77	>0.05
Asa			
1	18	19	>0.05
2	2	1	
Duration of anaesthesia (min.)	98.27±36.48	85.13±33.36	>0.05
Duration of surgery (min.)	89.18±27.14	75.12±25.52	>0.05

There was no significant difference in both the groups in reference to the baseline PR and the MAP.

At the end of infusion, the PR decreased highly significantly below the pre-infusion level in both the groups (P value < 0.05). 1 min. after intubation, the PR was still below the baseline value in both the groups. 1 min. after creating pneumoperitoneum, the rise in PR (above baseline) was significant in Dex 0.2 group (P value 0.005), while there was no rise in PR (as compared to baseline) in the other group. After extubation, PR rise in Dex 0.2 group, though rise was insignificant, and there was no rise in PR in Dex 0.4 even after extubation (Table 2).

Table 2: Changes in PR (beats per minute)

Time	Group Dex 0.2%	Group Dex 0.4%	P value
Before starting infusion	90.87±8.45	90.43±8.62	0.93
15 min. after starting infusion	82.56±3.24	80.09±4.67	0.11
1 min. after intubation	82.77±7.68	80.12±8.21	0.77
1 min. after pneumoperitoneum	98.34±4.32	87.45±8.13	0.008
1 min.	82.35±4.67	79.43±8.22	0.017

15 min.	79.67±5.45	77.12±10.23	0.008
30 min.	79.53±5.24	77.33±10.54	0.003
45 min.	80.22±5.68	77.20±10.33	0.012
60 min.	77.75±7.42	75.67±9.25	0.34
1 min. after release of pneumoperitoneum	76.79±4.78	76.12±8.24	0.02
1 min. after extubation	92.44±9.26	84.39±9.54	0.89

At the end of infusion, the MAP decreased in both the groups, but not significantly. No further significant changes were observed immediately after induction. After pneumoperitoneum and extubation, the MAP increased above the pre-infusion level in Dex 0.2 group (not significant), whereas in Dex 0.4 group, MAP remained below pre-infusion level even after intubation, pneumoperitoneum and extubation. Intubation did not produce a significant effect in both the Dex groups. Intraoperatively, MAP remained below baseline in both the groups but reduction was significant in Dex 0.4 (P value < 0.05) (Table 3).

Table 3: Changes in MAP (mm of Hg)

Time	Group Dex 0.2%	Group Dex 0.4%	P value
Before starting infusion	99.46±10.56	102.22±5.23	0.003
15 min. after starting infusion	95.56±9.78	93.09±6.89	0.13
1 min. after intubation	89.75±8.68	89.12±5.68	0.072
1 min. after pneumoperitoneum	102.33±12.32	95.43±7.13	0.021
1 min.	94.78±11.67	89.46±9.22	0.31
15 min.	97.67±10.45	91.12±10.21	0.92
30 min.	94.45±10.26	91.33±8.93	0.55
45 min.	93.67±11.68	90.57±8.33	0.14
60 min.	95.76±10.42	90.67±9.28	0.61
1 min. after release of pneumoperitoneum	93.59±11.78	87.12±9.24	0.29
1 min. after extubation	105.39±12.26	98.34±7.53	0.04

The rescue analgesia was required early (172 min.) in Group Dex 0.2 compared to group Dex 0.4 (248 min). 5 out of 20 patients in group Dex 0.2 and 9 out of 20 patients in group Dex 0.4 did not require rescue analgesia in first 24 hours (Table 4).

Table 4: Post-operative analgesic requirements

Group	Time for first rescue analgesic requirement (min.)	Cumulative analgesia requirement in 24 hours (mg.)
Group Dex 0.2	172 min. (5 patients did not require any analgesia in first 24 hours.)	115 mg
Group Dex 0.4	248 min. (9 patients did not require any analgesia in first 24 hours.)	97.3 mg.

Discussion

Dexmedetomidine exhibits a unique pharmacological profile with sedation, sympatholysis, analgesia and haemodynamic stability along with the great advantage of avoiding respiratory depression. Dexmedetomidine offers a dose-dependent cooperative sedation which allows interaction with the patient. These above-said aspects of the pharmacological profile of Dexmedetomidine render it suitable as an anaesthetic adjuvant and also for ICU sedation.

Dexmedetomidine is an imidazole compound, d- enantiomer of medetomidine with highly selective alpha2 agonism. The α2A adrenoceptors are mainly distributed in the periphery, while α2B and α2C are in the brain and spinal cord. Postsynaptic alpha2 receptors produce peripheral vasoconstriction, while presynaptic alpha2 receptors inhibits the release of noradrenaline, potentially attenuating the vasoconstriction. The overall response to alpha 2 receptor agonism is associated with stimulation of alpha 2 receptors located in CNS. These receptors are involved in the sympatholysis, sedation and antinociceptive effects of alpha2 receptors[4].

Dexmedetomidine with selective alpha2 agonism has a primary action on locus coeruleus[5]. Neuronal hyperpolarisation is a major component in mechanism of action of alpha2 agonist. The stimulated alpha2 receptors in substantia gelatinosa of dorsal horn of spinal cord inhibits nociceptive neuronal firing which are stimulated by the peripheral A, B and C fibres and also cause inhibition of secretion of nociceptive neurotransmitter- substance P.

Looking at these pharmacological properties, it has been evaluated in the past to assess its effect on haemodynamic responses in patients undergoing laparoscopic surgeries. The molecule has been used in infusion form with or without bolus dose. Infusion rates varying from 0.1 to 10 mcg/kg/h[6-8] have been studied. However, with higher dose infusion of Dexmedetomidine, high incidence of adverse cardiac effects have been observed[8]. A biphasic response on blood pressure occurs with a bolus dose[9]. Initially, there occurs hypertension followed by fall in blood pressure. This response is seen often more in young and healthy patients[10]. Stimulation of α2 B receptors in vascular smooth muscles is said to be responsible for this.

Low dose infusion of 0.25–0.5 mcg/kg/h results in a monophasic response of 10–15% fall in mean arterial blood pressure and PR[9]. Furthermore, in low dose, Dexmedetomidine exhibits linear kinetics, meaning that a constant amount of drug is eliminated per hour rather than a constant fraction of drug.

The basic effects of alpha2 agonism on the cardiovascular system was reduced heart rate, reduced systemic vascular resistance, and indirectly reduced myocardial contractility, systemic blood pressure and cardiac output. A bolus intravenous injection of 2 µg/kg resulted in an initial rise in blood pressure (22%) and reduction in heart rate (27%) from baseline that happened at 5 minutes after the administration. This initial rise in blood pressure is possibly caused by vasoconstrictive effects of Dexmedetomidine by stimulation of peripheral alpha2 receptors. Heart rate returned to baseline in 15 minutes, and blood pressure gradually reduced to approximately 15% below baseline in 1 hour. After an IM injection of the same dose, the initial rise in blood pressure was not seen; and heart rate and blood pressure remained within 10% of baseline[11].

Ebert and colleagues[12] performed an elegant study in healthy subjects using a target- controlled infusion system so as to provide rising concentrations (0. 7 to 15 ng/ m L) of Dexmedetomidine. They concluded that increasing concentrations of Dexmedetomidine in humans resulted in progressive increases in sedation and analgesia, decreases in heart rate, cardiac output, and memory. Eisenach JC, et al studied Dexmedetomidine CSF pharmacokinetics in sheep and correlated CSF concentrations to hemodynamic effects. They concluded that Dexmedetomidine appears rapidly in CSF after epidural administration and decreases BP[13]. Hogue, et al determined the effects of Dexmedetomidine on systemic and cardiac autonomic reflex responses during rest and thermal stress. They concluded that infusion of Dexmedetomidine in healthy subjects also resulted in compensated decrease in systemic sympathetic tone without causing change in baroreflex sensitivity. It also blunts the heart rate and systemic sympathetic activation owing to sweating but is less efficient in reducing cardiac sympathetic response to shivering[14].

Riker and colleagues found that the incidence of hypotension and bradycardia can be related to administration of a loading dose. Avoiding the loading dose or not giving more than 0.4 mcg/kg decreases the incidence of hypotension, or makes it less pronounced.

Giving loading dose over 20 minutes also reduces the transient hypertension[15]. In several studies after IM and IV administration, Dexmedetomidine caused, in a small percentage of patients, profound bradycardia (<40 beats/min) and occasionally sinus arrest/ pause. These episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergics. It would be expected from its profile that Dexmedetomidine would be beneficial to the ischemic myocardium. In animal models Dexmedetomidine showed some beneficial effects on the ischemic myocardium through decreased oxygen consumption and redistribution of coronary flow from non ischemic zones to ischemic zones after acute brief occlusion[16]. Dexmedetomidine also decreases serum lactate in a dog model of coronary ischemia with an associated reduction in heart rate and measured catecholamines. It also produced a rise in the endocardial/ epicardial blood flow ratio by 35%[17].

The perioperative use of alpha2 agonists reduces the incidence of perioperative myocardial ischemia[18]. More recently, Wallace and associates showed that administration of clonidine in the preoperative period reduces the incidence of perioperative cardiac ischemia from 31% to 14 %, and reduces the mortality for 2 years from 20% to 15% compared with placebo. The only data on potential benefits in perioperative ischemia prevention with Dexmedetomidine are provided in an underpowered study in vascular surgery patients who received the drug in the perioperative period. Blood pressure and heart rate were lower in the Dexmedetomidine group. No reductions of ischemic events were noted. No rebound effects were found when discontinuing Dexmedetomidine drip, even when it is given for more than 24 hours[19].

Hence, in a pilot study, we used low dose infusions of Dexmedetomidine without any bolus. Initially, we used Dexmedetomidine 0.2 mcg/kg/h infusion. Though it controlled the rise in PR and MAP at pneumoperitoneum, the control was not very effective at the time of tracheal intubation and extubation, and the PR and MAP both increased above pre-infusion levels. Hence, we increased the dose to 0.4 mcg/kg/h infusion in our next two patients. The results were quite satisfactory with this dose regimen. PR and MAP were always below pre-infusion levels in Dex 0.4 group.

Dexmedetomidine has been found to reduce the intra and post-operative requirement of opioids[20-22]. This effect of Dexmedetomidine is classically described as opioid sparing effect. We also observed an increase in the time to receive first rescue analgesia and a decrease in total analgesic requirements in first 24 h post-operatively in both Dexmedetomidine groups.

Conclusion

Therefore, it was concluded that Dexmedetomidine infusion in the dose of 0.4 mcg/kg/h more effectively attenuates haemodynamic stress response, as compared to dose of 0.2 mcg/kg/h, during laparoscopic surgery. And it was also concluded that the post operative analgesic requirement was significantly lower in dose of 0.4 mcg/k/h as compared to dose of 0.2 mcg/kg/h.

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