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EFFICACY OF LOW DOSE DEXMEDETOMIDINE INFUSION ON HAEMODYNAMIC STRESS, ANALGESIA AND SEDATION WITH SPECIAL REFERENCE TO LAPROSCOPIC ABDOMINAL SURGERIES

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ABSTRACT

Background: Nitroglycerine, beta-blockers and opioids are used in laproscopic surgeries as they provide hemodynamic stability during pneumo-peritoneum, but now less commonly used due to their disadvantages. **Aims and Objective:** To assess use of low dose dexmedetomidine infusion on post-operative analgesia requirements, sedation levels, haemodynamic response, and occurrence of adverse effects in patients undergoing laparoscopic surgery. **Material and Methods:** In the present study the patients included were randomly divided into three groups of 15 patients each, Group A (patients receiving normal saline 0.9% infusion), Group B (dexmedetomidine infusion 0.2 mcg/kg/h) and Group C (dexmedetomidine infusion 0.4 mcg/kg/h). **Result:** The pulse rate and mean arterial blood pressure was not effective at the time of pneumoperitoneum and when we increased the dose of dexmedetomidine to 0.4 microgram per kg per hour, the result were satisfactory. First rescue analgesia is required after more time compared to group A patients. Total analgesic requirements in first 24 h post-operatively is also found to be decreased in both dexmedetomidine groups i.e. group A and B. **Conclusion:** Low dose infusion of dexmedetomidine provides lighter sedation and reduces the post-operative analgesic requirements without any significant adverse effects.

KeyWords : Dexmedetomidine, Pulse rate, Mean arterial pressure, haemodynamic stress

INTRODUCTION

Among interventional procedures laproscopic techniques are the most commonly used technique now a day as it minimizes trauma, stress, hospital stay, morbidity, postoperative pain and requirement of analgesic. They cause rapid return of gastrointestinal function, earlier returns to normal activities, less postoperative ileus compared to traditional open surgeries as well as improved postoperative pulmonary function.

The operative technique includes insufflations of CO_2 in the abdominal cavity with intra-abdominal pressure of 10-15 mmHg with range of 0 30 mm of Hg and flow rate 0 9.9 litre per minute. **(1)** Hypercapnia and respiratory acidosis can occur due to absorption of CO_2 from the peritoneal cavity. Both pneumo-peritoneum and CO_2 causes elevated arterial pressure, raised pulmonary artery occlusion pressure, increased systemic vascular resistance and decreased cardiac output due to

increase in catecholamine level which finally affect renin-angiotensin-aldosterone-system.

Nitroglycerine, beta-blockers and opioids are used in laproscopic surgeries as they provide hemodynamic stability during pneumo-peritoneum, but now less commonly used due to their disadvantages. **(2)** Remifentanyl preferably used for infusion, provides better control of hemodynamic responses compared with alfentanyl as it is rapidly hydrolysed by tissue and nonspecific esterases.

Clonidine and Dexmedetomidine are α-2-adrenergic agonists .The hemodynamic stability of clonidine is better in patients with compromised cardiac function.

Dexmedetomidine, an imidazole derivative, introduced in 1999, are known to produce analgesia, hypnosis, sedation, sympatholytic effects, decrease opioid induced muscle rigidity along with supraspinal, spinal, and peripheral actions, anxiolytic property and without producing significant respiratory depression. **(4)**

Dexmedetomidine had a relatively high ratio of α2/α1-activity (1620:1 compared with 220:1 for clonidine) may result in more potent effects of sedation, dose-dependent decrease in arterial blood pressure (ABP) and heart rate (HR) associated with a low level of serum noradrenaline concentration. **(5, 6)** Dexmedetomidine, in a single pre-anesthetic intravenous dose of up to 0.6μg/kg, causes reduction in the requirement of supplemental isoflurane administration during nitrous oxide/oxygen, fentanyl anaesthesia and lessen haemodynamic reaction to stressful intra-operative events with few side-effects. **(7)**

The aim of our study was therefore, to assess use of low dose dexmedetomidine infusion on post-operative analgesia requirements, sedation levels, haemodynamic response, and occurrence of adverse effects in patients undergoing laparoscopic surgery.

MATERIAL AND METHODS

The present study was a placebo controlled randomized, double blind, prospective clinical trial. A written informed consent was also taken from patients included in the study after fulfilling inclusion criteria. Those who were not fit as per exclusion criteria were excluded from the study.

Inclusion crieteria

Forty five ASA physical grades I and II patients between the age of 18 and 50 years, of either sex and posted for laparoscopic surgeries under general anesthesia were included in the study.

Exclusion crieteria

- Patients with history of allergy drugs particularly α2 agonists
- Patients on drugs like β blockers or calcium channel blockers
- Patients with decreased autonomic control such as the elderly
- Patients with chronic hypertension
- Patient with ASA physical status III , AV block, morbid obesity
- Patients with severe cardiac, renal or hepatic disease
- Patients with Diabetes
- Pregnant or lactating women
- Patients with history of allergy to egg proteins
- Patients refused to be included in the study

The patients included in the study were randomly divided into three groups of 15 patients each, Group A (patients receiving normal saline 0.9% infusion), Group B (dexmedetomidine infusion 0.2 mcg/kg/h) and Group C (dexmedetomidine infusion 0.4 mcg/kg/h).

Infusion was prepared as per the group allocated in separated operation theatre. Dexmedetomidine 0.5 ml containing 50 μg of the drug was withdrawn in a 20 ml and diluted with 12 ml of normal saline to form final concentration 4 mcg/ml of solution. Dexmedetomidine or normal saline infusion was given by syringe infusion pump (covered with cloth for hiding the group from assessor and patient) at target infusion rate depending on weight of patient. Decoding of blinding was done at the end for tabulation and result analysis.

In operation theatre, a multi-para monitor was attached for pulse rate (PR), mean arterial pressure (MAP) and oxygen saturation. Intravenous fluid was inserted through wide bore canula with another line for infusion pump. Glycopyrrolate 5 mcg/kg IM and injection tramadol 1.0 mg/kg IM were administered 30 min before as premedication. Injection ranitidine 50 mg IV

and injection ondansetron 4 mg IV was given at the time of induction.

Induction was started with injection propofol 2 mg/kg IV followed by injection succinyl choline 1.5 mg/kg IV. Patient was intubated and anaesthesia was maintained with O2:N_2O (1:1 ratio), isoflurane and injection vecuronium bromide as a muscle relaxant. All were stopped at the end of surgery. Intra-abdominal pressure was maintained between 10 and 15 mmHg throughout the laparoscopic procedure. Patients were mechanically ventilated using circle system to keep the $EtCO_2$ between 35 and 45 mm Hg. Reversal and extubation were carried out by conventional methods. Injection ondanseteron 4mg was given before reversal by neostigmine 0.05 mg/kg and glycopyrrolate 0.02 mg/kg and patient was extubated. After extubation, time to response to verbal commands was recorded. Post-operatively 100% oxygen was given by face mask for 15 mins.

All the patients were observed for vital parameters like pulse rate, mean arterial pressure and oxygen saturation (SpO_2) at regular intervals i.e. before starting the infusion, 15 min after starting the infusion, after induction, after intubation, after creation & release of pneumo-peritoneum and after extubation. Patients were also observed for post-operative sedation level, time to first rescue analgesic requirement (time from completion of injection of drug to the time post-operatively when pain reported by patient was ≥ 4 on VAS i.e. visual analogue scale), 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. Sedation was assessed at 5, 15, 30, 60 to 120 min post-operatively using Ramsay sedation score (RSS).

Patients were observed for any adverse effects like bradycardia, tachycardia (PR less than or more than 20% of pre-operative level respectively on two consecutive readings), hypo and hypertension (MAP less than or more than 20% of pre-operative level respectively on two consecutive readings), sedation score more than RSS 4, respiratory depression (SaO_2 < 90%) and dryness of mouth and they were managed conventionally.

The results were tabulated and statistically analyzed using SPSS (Statistical Package for Social Sciences) Software version 19.0, Chi-square test was used for qualitative data (sex, ASA grade), pulse rate, blood pressure, oxygen saturation (SpO_2), end tidal carbon dioxide etc., were compared within the group against baseline values using paired t-test. P >0.05 was considered insignificant, <0.05 as significant and highly significant if <0.001.

RESULT

In relation to age, sex, weight, ASA grading, duration of anesthesia and duration of surgery the group A, B & C were nearly comparable. The p value was slightly higher in relation to ASA grading, duration of anaesthesia and duration of surgery. (Table 1)

Table 1: Demographic Variables with duration of Anaesthesia and surgery

Parameters	Group A %	Group B %	Group C %	Intergroup P
Age in years (mean±SD and range)	38.3 ± 4.6	39.1 ± 7.3	40.9 ± 5.5	-
Sex				-
Male	8 (53.3)	6 (40)	7 (46.7)	
Female	7 (46.7)	9 (60)	8 (53.3)	
Weight in kg (mean±SD and range)	56.3 ± 7.9	55.4 ± 3.7	54.4 ± 5.3	-
ASA				
1	13 (84.6)	14 (93.3)	13 (84.6)	> 0.05
2	2 (15.4)	1 (6. 7)	2 (15.4)	
Duration of anaesthesia (in min)	85.2 ± 20.6	90.7 ± 28.5	79.4 ± 26.6	> 0.05
Duration of surgery (in min)	68.6 ± 19.2	72.4 ± 22.4	61.8 ± 18.9	> 0.05

In group A the changes in pulse rate and mean arterial pressure were of insignificant nature, there is slight increase occurs after extubation was found. (Tables 2 & 3).

Table 2: Changes in PR (beats per minute) (mean±SD)

Time	Group A	Group B	Group C
Before starting infusion	89.3 ± 5.9	91.6 ± 7.6	90.8 ± 7.5
15 min after starting infusion	88.6 ± 4.1	83.5 ± 5.3	80.6 ± 6.9
1 min after induction	87.3 ± 3.6	83.2 ± 8.6	80.4 ± 8.9
After laryngoscopy and intubation	105.3 ± 6.8	99.3 ± 5.1	86.9 ± 8.5
After pneumoperitoneum			
5 min	92.7 ± 4.8	82.5 ± 5.1	78.6 ± 9.8
15 min	91.6 ± 4.9	79.8 ± 5.7	76.9 ± 10.1
30 min	90.2 ± 5.1	79.7 ± 5.9	76.6 ± 10.6
45 min	88.3 ± 4.7	80.6 ± 5.4	77.2 ± 10.9
60 min	88.7 ± 4.6	77.3 ± 5.1	75.6 ± 9.9
After release of pneumoperitoneum	85.3 ± 4.1	76.3 ± 3.8	76.2 ± 7.9
After extubation	103.2 ± 7.9	93.1 ± 9.2	83.7 ± 8.9

Better control of pulse rate and mean arterial pressure was found in group C i.e. dexmedetomidine infusion 0.4 mcg/kg/h compared to group B i.e. dexmedetomidine infusion 0.2 mcg/kg/h 15. 15 min after starting infusion, 1 min after induction, 1 min after induction, After pneumoperitoneum 5 min, 15 min, 30 min, 45 min, 60 min, After release of pneumoperitoneum and after intubation in all the parameters group C control was more in benefit of patient.

Table 3: Changes in MAP (mm of Hg) (mean±SD)

Time	Group A	Group B	Group C
Before starting infusion	99.3 ± 9.2	99.2 ±	102.1 ± 4.2
15 min after starting infusion	98.6 ± 4.3	94.9 ±	94.1 ± 3.5
1 min after induction	98.7 ±5.2	89.3 ±	89.6 ± 3.6
1 min after induction	112.8 ±8.9	104.2 ±	94.9 ± 8.3
After pneumoperitoneum			
5 min	102.5 ± 8.6	94.6 ± 11.9	89.6 ± 4.3
15 min	100.1 ± 8.1	97.8 ± 8.3	92.0 ± 8.2
30 min	96.2 ± 3.5	94.3 ± 5.6	91.6 ± 7.7
45 min	96.7 ± 5.4	93.6 ± 5.3	90.3 ± 7.3
60 min	95.5 ± 5.3	96.1 ± 8.6	90.8 ± 4.5
After release of pneumoperitoneum	94.8 ± 8.1	93.2 ± 11.8	87.9 ± 9.4
After extubation	115.1 ± 10.8	105.9 ± 13.5	95.6 ± 6.7

After extubation, the pulse rate and mean arterial pressure increased significantly above the pre-infusion level in group A, compared to increase in group B ($P < 0.05$). While the pulse rate and mean arterial pressure in group C was below the pre-infusion level ($P < 0.05$).

The mean sedation score was better in group B & C, compared to group A. Group C patients had better sedation score, cooperative, oriented and tranquil as compared to group B. In group A with time better sedation score was achieved due to early use of analgesia.

Table 4: Changes in mean sedation score

Group	Post operative (mean)					
	1 min	15 min	30 min	45 min	60 min	120 min
Group A	1.3	1.5	1.75	1.8	1.85	1.9
Group B	2.1	1.8	1.9	2.05	2.0	2.05
Group C	2.9	2.5	2.2	2.1	2.15	2.1

First rescue analgesia as well as cumulative dose of analgesia was required after more duration and less dose respectively in case of group C while it is required in group A within one hour with a higher dose. (Table 5)

Table 5: Post-operative analgesic requirements

Group	Time for first rescue analgesia	Cumulative analgesia in 24 h
Group A	48 min	300.0 mg
Group B	163 min (3 patients need no analgesia in 24 hours)	120 mg
Group C	257 min	85 mg

DISCUSSION

Dexmedetomidine is a highly selective alpha 2 agonist act through three types of alpha 2 receptor – 2 A, 2 B and 2 C in the brain and spinal cord leads to sedation, analgesia, anxiolysis and sympatholysis that finally leads to hypotension and bradycardia. Suppression of norepinephrine and substance P release is a related with the various actions of Dexmedetomidine. Therefore it is used in laparoscopic surgery.

It is used in infusion form rate varying from 0.1 to 10 microgram per kg per hour. **(8, 9, 10)** High dose of infusion is related with cardiac adverse effect. **(10)** Low dose infusion of 0.25 to 0.5 micro gram per kg per hour results in monophasic response of 10 to 15% fall in mean arterial blood pressure and pulse rate. **(11)** Hence in this study we use low dose dexmedetomidine in 0.2 microgram per kg per hour infusion. The pulse rate and mean arterial blood pressure was not effective at the time of pneumoperitoneum and when we increased the dose of dexmedetomidine to 0.4 microgram per kg per hour, the result were satisfactory. Therefore 0.4 mcg/kg/hour dose is the most satisfactory dose in all the three group i.e. group A, B and C for pulse rate and mean arterial blood pressure.

In our study all the three groups does not show any significant difference except for a mild difference in mean intubation time. Bhattacharjee et al **(12)** also observed no significant effect of dexmedetomidine on response to verbal command and extubation time. Dexmedetomidine has been found to reduce the intra and post-operative requirement of analgesia. **(10, 13, 14, 15)** Therefore first rescue analgesia is required after more time compared to group A patients. Total analgesic requirements in first 24 h post-operatively is also found to be decreased in both dexmedetomidine groups i.e. group A and B.

Critical incidences like laryngoscopy and intubation, pneumoperitoneum and extubation were responsible for significant rise in the mean arterial blood pressure and pulse rate in patients undergoing laparoscopic surgeries **(4, 16)** as seen in group A patients. Dexmedetomidine is also responsible for stress response attenuation, sedation and analgesia as seen in the study. Sedation is dose dependent and reaches peak in 45 60 min after observing the patient for 120 min. as the elimination half-life is 2 hours, unique in nature as the patient can be aroused easily, follow verbal command, cooperate in surgery and can be present in sleep like state.

CONCLUSION

Low dose infusion of dexmedetomidine at the rate of 0.4 mcg/kg/hour provides anaesthesia, control haemodynamic stress response to intubation, pneumoperitoneum and extubation, provides lighter sedation and reduces the post-operative analgesic requirements without any significant adverse effects in patients undergoing laparoscopic abdominal surgeries.

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