ORIGINAL ARTICLE

Comparison of Two Doses of Dexmedetomidine on Haemodynamic Stability in Patients Undergoing Laparoscopic Surgeries

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Abstract:

Background: Dexmedetomidine has gained its popularity in providing stable haemodynamics, with significant post operative analgesia and sedation in patients undergoing laparoscopic surgeries. Two different doses of dexmedetomidine boluses were used pre-operatively and studied the intra and post-operative effects. *Aim & Objectives:* To compare two doses (1.0 µg/kg or 0.7µg/kg) of dexmedetomidine infusion administered pre-operatively with regards to their haemodynamic, sedative and analgesic effect in patients undergoing laparoscopic surgeries. To study the effect of intravenous dexmedetomidine on post-operative analgesia. *Material and Methods:* 84 patients were randomly divided into two groups of 42 each. Group A received injection dexmedetomidine 1µg/kg, while group B received 0.7µg/kg; as an intravenous bolus dose in 48 ml NS over 15 min in preanesthesia room. Parameters assessed were Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Blood Pressure (MABP), Saturation of Oxygen (SpO_2), End Tidal Carbon Dioxide (Et CO_2), Respiratory Rate (RR); perioperatively, at regular intervals. In the post-operative period, intramuscular injection diclofenac 75 mg was used as a rescue analgesic. Postoperative pain and level of sedation were gauged with Visual Analog Scale (VAS) score and Ramsay scale respectively. Observations and *Results:* The hemodynamic stability, level of sedation achieved were better with Group A. The duration of post extubation analgesia observed in group A was significantly (P= 0.01) more. The adverse events noted in both the groups were very few. Conclusion: We hereby conclude that dexmedetomidine in a dose of 1µg/kg as pre operative bolus dose in patients undergoing lapararoscopic surgeries gives better haemodynamic stability, post operative analgesia, sedation and reduction in the dose of inhalational anesthetic agent compared to 0.7µg/kg dose without increase in the incidence of adverse effects.

Keywords: Dexmedetomidine, Haemodynamic stability, Laparoscopy, Pneumoperitonium

Introduction:

Laparoscopic surgery has considerable advantage over open surgeries in reducing post-operative morbidity and hospital stay. Since scarring is less, it produces less pain, morbidity and need of hospitalization. However, the enthusiasm for laparoscopic surgery has been tempered somewhat due to intra-operative physiologic complications like haemodynamic instability caused by the carbon dioxide pneumoperitoneum [1].

CO_2 pneumoperitoneum causes significant release of catecholamines, cortisol, renin-angiotensin-aldosterone and vasopressin, thus leading to; increase in Systemic Vascular Resistance (SVR) causing systemic hypertension, increase in Pulmonary Vascular Resistance (PVR), inotropic effects on heart, namely tachycardia [2]. Trendelenburg position given intraoperatively; increases intra-abdominal

pressure which in turn reduces venous return and cardiac output, leading to cardiac dysfunction.

Several drugs which include opioids like fentanyl, remifentanyl; alpha 2 agonists like clonidine, dexmedetomidine; antihypertensives like beta blockers, nitroglycerine infusions have been used to attenuate these responses. Dexmedetomidine is an imidazoline derivative which selectively acts on the alpha 2 receptors as an agonist. By attenuating sympathetic activity, it inhibits release and uptake of norepinephrine [3]. It acts through three types of α2 receptors-α2 A, α2 B and α2 C situated in brain and spinal cord. Stimulation of α2 A and α2 C in locus ceruleus causes sedation. In the spinal cord, activation of both α2 A and α2 C receptors directly reduce pain transmission by reducing release of substance P which produces analgesia [1, 3]. It increases cardiac baroreceptor sensitivity and also blunts stress response to surgical stimuli. This may help to reduce the narcotic and anaesthetic dose, as well as post operative analgesic requirement [3]. Review of literature suggests that several studies have been done on use of dexmedetomidine Infusions in the rates varying from 0.1-10 mcg/kg/h for evaluation of its effects on patients undergoing laparoscopic surgeries [4-7].

We have not come across a study on use of dexmedetomidine as a single bolus dose given preoperatively in the patients undergoing laparoscopic surgeries. We have planned our study to evaluate its effects on haemodynamics over period of two hours and decide maximum possible bolus dose which is safe and effective.

The study was planned to compare the effects of two different doses (1.0μg/kg and 0.7μg/kg) of dexmedetomidine as boluse doses on attenuation of hemodynamic changes when given as an adjuvant to general anesthetics as a primary outcome. The secondary outcome being evaluation of its effects on a dose requirement of an inhalation anesthetic agent, drug related incidence of perioperative adverse events and effect on postoperative analgesia in patients undergoing laparoscopic surgeries.

Material and Methods:

After obtaining Institutional Ethical Committee approval and informed consent of the patients, 84 patients of either sex, aged 18-50 years posted for laparoscopic surgery under general anesthesia were included in the study. Patients were randomly divided into two groups of 42 each. Group A received injection dexmedetomidine as an intravenous bolus dose of 1 μg/kg, while group B received 0.7μg/kg; in 48ml NS over 15 min in preanesthesia room.

The inclusion criteria for the study were: American Society of Anesthesiologists (ASA) grade I and II patients, Body Mass Index (BMI) between 20 and 30, patients undergoing general anesthesia, duration of laparoscopic surgery upto 2 hours.

The exclusion criteria for the study were: patients with cardiorespiratory disease, hypertension, ischemic heart disease, hypotension, heart blocks, and mental depression. Patients receiving medication that might interfere with demedetomidine action such as tricyclic antidepressants, monoamine oxidase inhibitors, nitroglycerine, labetalol or any other antihypertensive, hypersensitivity or allergy for the drug were excluded.

Bradycardia or hypotension of more than 20% of the baseline were considered significant and treated with injection atropine 0.6mg and injection ephedrine 3mg aliquots respectively.

All patients were preloaded with 500 ml of normal saline to prevent sudden hypotension. Anesthesia procedure involved pre-oxygenation with 100% oxygen for 5 min, intravenous induction with propofol 2µg/kg, fentanyl 2µg/kg and atracurium 0.5 mg/kg as induction doses, intubation with Portex ®endotracheal tube, maintenance on O_2(50%):N_2O(50%) with dial concentration of sevoflurane adjusted to maintain adequate depth of anesthesia.

At the end of surgery, reversal with injection neostigmine 0.04mg/kg and injection glycopyrrolate 10mcg/kg was done. Intravenous paracetamol 1g was given 30-45 min after induction of anesthesia for the purpose of postoperative analgesia.

Parameters assessed were heart rate, systolic, diastolic and mean arterial pressures, Oxygen saturation, end tidal CO_2 concentration and respiratory rate. They were noted as baseline parameters prior to the administration of the study drug in preanesthesia room; pre-induction; post-intubation, at regular intervals 10, 15, 30, 45, 60, 75, 90, 105 and 120 min during operation and every 15 min for 2 hrs after extubation. Capnography monitoring in the post-intubation period was carried out and the patients were ventilated accordingly to maintain $paCO_2$ levels between 35 and 45mmHg.

In the post-operative period when Visual Analog Scale (VAS) score was 3 or above, the patient received a rescue dose of analgesic in the form of injection diclofenac 75mg given intramuscularly. The time to first rescue analgesic was noted in minutes. The level of sedation in the postoperative period was assessed by Ramsay scale.

Deviation in the HR or the MABP >20% from the baseline was considered significant and was treated immediately. Bradycardia was treated with injection atropine 0.6mg. Hypotension was treated with intravenous fluids with or without injection ephedrine. Hypertension was treated with nitroglycerine infusion. The safety of the procedure was assessed by the occurrence of any adverse events and the requirements to pharmacological support. The abdominal pressures were monitored during insufflations; it was not allowed to exceed 14mmHg with maximum allowable flow rate of CO_2 to be maintained at 2 L/min.

Taking power 0.8 and alpha error 0.05, a minimum sample size of 40 patients was calculated for each group. The total number of patients in each group was 42 to compensate for possible dropouts.

Statistical Analysis:

The data was compiled and subjected to the statistical analysis. Unpaired t-test was used for intergroup comparison. Hemodynamic parameters and numerical data were compared within the group against baseline values using paired t-test. Categorical data (HR, blood pressure, oxygen saturation, end tidal carbon dioxide) was analyzed by Chi-square test. For comparison of continuous data such as hemodynamic parameters ANOVA test was used. The results were expressed as Mean ± Standard Deviation (SD), $p \leq 0.05$ was considered to be significant. Statistical package for social sciences (SPSS) version 15.0 for windows was used for statistical analysis.

Results:

Of the 84 patients who were enrolled in the study, 2 patients from group A and 1 from group B were excluded as their surgery extended beyond two hours. The demographic data that is age, sex, ASA grades, weight, height, BMI and surgical duration matched for both groups in (Table 1).

Table 1: Demographic Data of Groups

Parameters		Group A (N=40)	Group B (N=41)	P value
		Mean ± SD	Mean ± SD	
Age		34.1 ± 12	36.07 ± 10	0.44
Sex	Female	55%	62%	0.22
	Male	45%	38%	-
Weight (kg)		64.3 ± 12.05	63.5 ± 11.57	0.75
Height (cm)		162.6 ± 9.2	164.0 ± 8.7	0.12
BMI		23.79 ± 2.5	24.28 ± 2.7	0.47
ASA	I	75%	71%	0.45
	II	25%	29%	-

Intergroup comparison of baseline haemodynamic parameters (HR, BP, Oxygen saturation) revealed that both the groups were comparable.

Compared to baseline values, reduction in the heart rate was observed in both the groups; maximum after 30 min of administration of study drug; the time interval coinciding with preinduction values. The heart rate was reduced to statistically significant level at preinduction period in Group A and remained at lower levels throughout the operation (Fig.1).

Compared to baseline values, reduction in the MABP was statistically insignificant in both the groups; maximum reduction was observed for 10 min in postintubation period. However, values of MABP in Group A never crossed above baseline values till end of the surgery (Fig. 2).

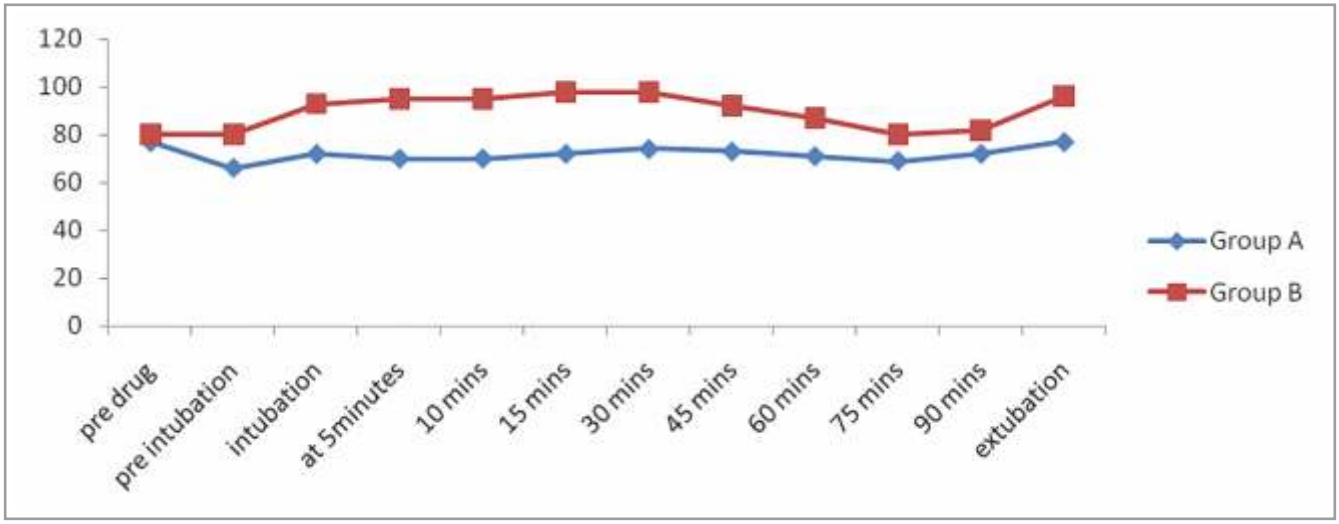

Fig. 1: Comparison of Intraoperative Variations in Heart Rates

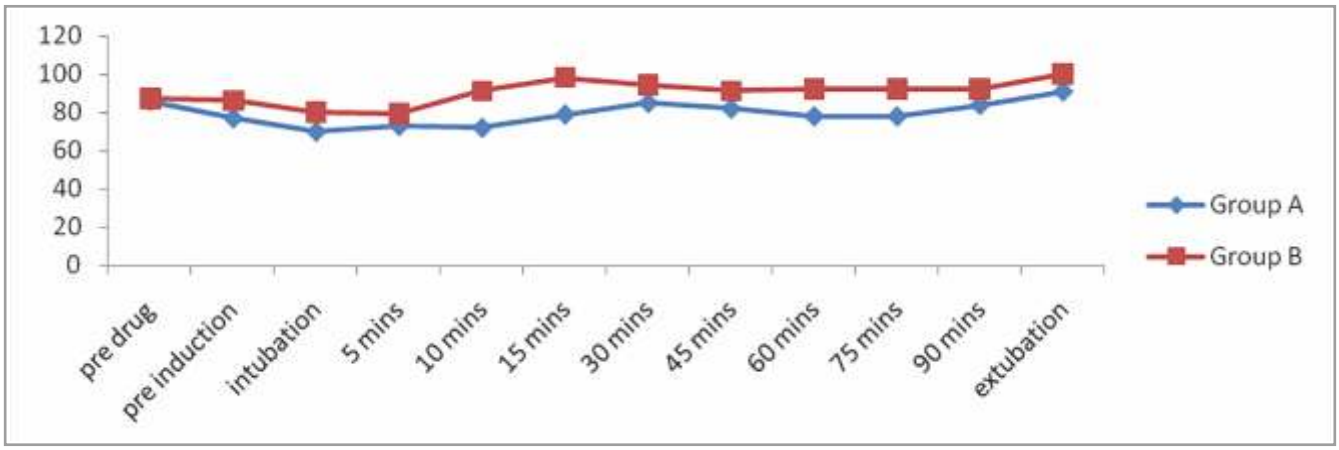

Fig. 2: Comparison of Intraoperative Variations in Mean Arterial Pressures

The post extubation VAS scores differed significantly (P= 0.01) with scores being higher in group B which co-related with the time interval of first rescue analgesic being less in group B (Table 2).

The mean time duration required for first analgesic dose in group A was 33 ± 8.6 min compared to 10 ± 2 min in group B (P< 0.001) (Table 3).

The dial concentration of sevoflurane did differ significantly in both groups, concentrations being less in group A (p= 0.001) (Fig.3).

Table 2: Visual Analog Scale Scores

VAS	A	%	VAS	B	%
0	16	57.1	0	4	14.3
1	10	39.3	1	8	35.7
2	1	3.6	2	14	50
Total	27	100	Total	26	100

Table 3: Rescue Analgesic Doses

Time for first analgesic (in min)	A	B	P value
Mean	33	10	0.001
Median	32	12	
SD	8.6	2.8	

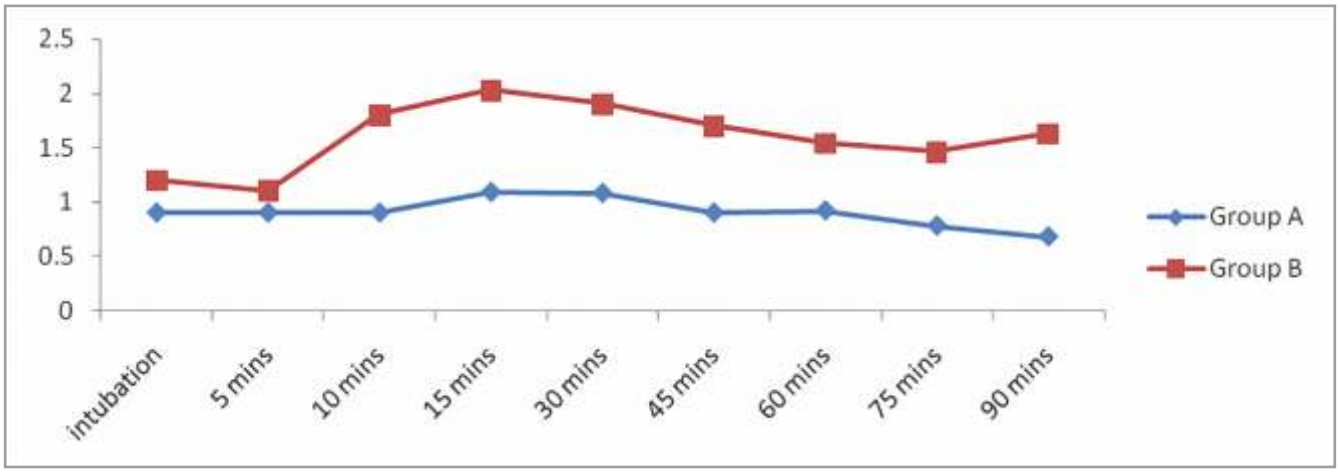

Fig. 3: Comparison of Intraoperative Dial Concentration of Sevoflurane

The post operative sedation scores were measured according to Modified Ramsay scale. There was no significant difference in the sedation scores of the two groups. The patients in group A were more sedated (P= 0.000) compared with group B, however did not exceed a score of 2. The SpO_2 remained same in both the groups. The RR and end-tidal CO_2 did not vary in both groups throughout the surgery.

Adverse events:

2 patients (6.67%) from group B showed extreme hypertensive response immediately after giving infusion requiring nitroglycerine infusion. One patient (3.33%) from group A developed bradycardia (HR: 55beats/min) which occurred after 30 min of infusion and was treated with injection Atropine 0.6 mg immediately.

During the study none of the patient had any drug related adverse reaction. At no point of time the sedation levels achieved in both the groups were more than four requiring additional oxygen supplementation to maintain airway. There was no morbidity or mortality found in the study subjects.

Discussion:

CO_2 pnemoperitoneum during laparoscopy is associated with significant haemodynamic changes such as increase in MABP, SVR and decrease in cardiac output necessitating preloading or other appropriate therapeutic interventions [2, 3]. Dexmedetomidine is a highly selective $\alpha 2$ agonist and has a significant sympatholytic property. It causes dose-dependent decrease in heart rate and blood pressure. Previous studies have shown that dexmedetomidine attenuates stress response to intubation by decreasing central sympathetic outflow, thereby decreasing serum epinephrine and norepinephrine levels [8, 9].

Looking at these pharmacological properties, the molecule dexmeditomidine has been used in infusion form with or without bolus dose to assess its effect on haemodynamic responses in patients undergoing laparoscopic surgeries. Gourishankar *et al* [4] have used low dose infusion of dexmedetomidine at the rate of 0.4mcg/kg/h without any bolus dose, in patients undergoing laparoscopic cholecystectomy. They found that the drug serves as a very useful anaesthetic adjuvant to control haemodynamic stress response to intubation, pneumoperitoneum and extubation. It also provides lighter sedation and reduces the post-operative analgesic requirements without any significant adverse effects [3, 4]. In a similar study, Vora *et al* have demonstrated that an infusion of dexmedetomidine (0.5mcg/kg/h) is also effective and safe for attenuation of increase in HR and BP due to stress response of laparoscopic surgery [7].

Review of literature suggests that infusion rates varying from 0.1 to 10mcg/kg/h have been studied. However, with higher dose infusion of dexmedetomidine, high incidences of adverse cardiac effects have been observed [10]. Vikas Kumar *et al* [11] have in their study on patients undergoing middle ear surgeries under local anesthesia also used a single bolus dose of 1 mcg/kg and concluded that a maintenance dose of dexmedetomidine (0.2-1mcg/kg/hr) is needed for surgeries requiring more than 60 min.

A recent study by Rabie Soliman and Gomaa Zohry have demonstrated that a loading dose of 1mcg/kg over 15 min before induction and maintenance with 0.3mcg/kg/h of dexmedetomidine infusion is safe for cardiac patients undergoing laparoscopic cholycystectomy. It attenuated the changes in heart rate and blood pressure and decreased the total dose of fentanyl and end-tidal sevoflurane and the requirement for medications in high risk cardiac patients [6].

A biphasic response on blood pressure occurs with a bolus dose. Initially, there occurs hypertension followed by fall in blood pressure.

This response is seen often more in young and healthy patients. Stimulation of α2 B receptors in vascular smooth muscles is said to be responsible for this.

We have aimed to study a single dose of dexmedetomidine in preoperative period for its efficacy and safety as an adjuvant to general anesthetic sevoflurane to evaluate the effects on degree of attenuation of pressor response to various stimuli throughout the laparoscopic surgeries. We have also studied its effects on postoperative analgesia, sedation, adverse events, dose of inhalational anesthetic and have compared them to decide which dose (1mcg/kg or 0.7mcg/kg) is more effective yet safe. To avoid initial rise in the BP, we have diluted the drug in 48 ml of NS to make the concentration as 4mcg/ml and the calculated dose has been given slowly over 15 min.

Lawrence and De Lange have investigated the effect of a single pre-induction intravenous dose of dexmedetomidine 2μg/kg on anaesthetic requirements and peri-operative haemodynamic stability in patients undergoing minor orthopaedic and general surgery. They have found that the hypotension and bradycardia occurrence has been more frequently after dexmedetomidine [12].

Ghodki *et al* [5] have monitored the Depth of Anesthesia (DOA) using entropy in the patients undergoing laparoscopic surgeries under general anesthesia. They have used a loading dose of dexmedetomidine as 1mcg/kg for 15 minutes and maintenance infusion of 0.2mcg/kg/hr. They have found 62.5% reduction (0.75mg/kg) in the induction dose of propofol, with a 30% less end-tidal concentration of isoflurane requirement for maintenance of anesthesia, while maintaining the adequate DOA. They have concluded that Dexmedetomidine is an effective anesthetic adjuvant that can be safely used in laparoscopy without the fear of awareness under general anesthesia [5].

Tufanogullari *et al* [13] in their dose-ranging study of dexmedetomidine infusion (0.2, 0.4, and 0.8mcg/kg/h) have recommended the infusion rate of dexmeditomidine to be 0.2mcg/kg/h to minimize the risk of adverse cardiovascular side effects. They have also noted that the use of dexmeditomidine could reduce the average end-tidal desflurane concentration by 19, 20, and 22%, respectively. However as per their observations, it has failed to facilitate a significantly faster emergence from anesthesia on both early and late recovery after laparoscopic bariatric surgery.

In our study, we too have noted that dexmeditomedine in a dose of 1μg/kg and 7mcg/kg reduces requirment of sevoflurane to produce adequate depth of anesthesia. However, due to non availability of gas analyser, we could not quantify this finding.

Yildiz *et al* [10] have evaluated the effect of a single pre-induction intravenous dose of dexmedetomidine 1mcg/kg on cardiovascular response resulting from laryngoscopy and endotracheal intubation, need for anaesthetic agent and perioperative haemodynamic stability on patients undergoing minor surgeries under general anesthesia. In their study they have concluded that single dose of dexmedetomidine in preoperative period decreases blood pressure and heart rate during laryngoscopy, reduce opioid and anaesthetic requirements and enhances speed of recovery postoperatively.

Our results are also in line with their observations. We have observed that dexmedetomidine in a dose of 1μg/kg could effectively attenuate the vasopressor response of laryngoscopy, and intubation and the sympathoadrenal response occurring with pneumoperitoneum.

Hall, Uhrich *et al* in their research have determined the safety and efficacy of two small-dose infusions (0.2 and 0.6mcg/kg) of dexmedetomidine by evaluating sedation,

analgesia, cognition, and cardiorespiratory function. Dexmedetomidine infusions have resulted in reversible sedation, mild analgesia, and memory impairment without cardiorespiratory compromise [14]. We have also found that dexmedetomidine significantly reduces the need of post operative analgesics. In our study, dexmedetomidine in a dose of 1µg/kg has provided better pain relief and sedation than at the dose of 0.7µg/kg without compromising safety.

Dexmedetomidine infusions have been used for ICU sedation for 24 hours. It is said to mainly act through α2b receptors mimicking natural sleep and quick arousal [15, 16]. In our study, the sedation scores noted in both groups confirm the same, moreover there has been no oversedation requiring intervention to maintain airway.

The activation of α2 adrenoceptors, imidazoline-preferring receptors, or both in the ventrolateral medulla and especially in the solitarius nucleus tract by dexmedetomidine causes bradycardia [12, 17]. In our study we have found one patient from group A developing significant bradycardia, which has been treated with injection Atropine 0.5mg.

Bajwa *et al* [18] have explored the effectiveness of dexmedetomidine in suppressing the post-anesthetic shivering in patients undergoing for laparoscopic surgical procedures under general anesthesia. Their research has shown that intraoperative dexmeditomidine infusion in a dose of 1µg/kg is helpful in alleviation of post operative shivering, nausea and vomiting.

In the two phase multicentric, randomized, double blind trial namely the MIDEX trial comparing midazolam with dexmedetomidine and the PRODEX trial comparing propofol with dexmedetomidine in ICUs has measured proportion of time at target sedation level by Richmond Agitation-Sedation Scale and found that dexmedetomidine is not inferior to midazolam and propofol in maintaining light to moderate sedation. Dexmedetomidine has reduced duration of mechanical ventilation compared with midazolam and has improved patients' ability to communicate pain compared with midazolam and propofol. However, they have found more adverse effects associated with dexmedetomidine (dose range 0.2-1.4µg/kg/hr) [19].

Chrysostomou and Schmitt in their review article have elaborated the current use of dexmedetomidine in adult and pediatric populations in several clinical settings, including operating room, intensive care unit, postsurgical patients and patients who needed sedation and/or analgesia for invasive and noninvasive procedures. They have also commented upon its promising future applications in the areas of neuroprotection, cardioprotection and renoprotection [15].

Limitations:

A control group has not been included in the study. Dial concentration of sevoflurane does not give the exact amount of gas delivered. End tidal gas concentration analysis would have helped us better in estimation of percent dose reduction of volatile anesthetic agent when dexmeditomidine is used as a premedicant. We could not estimate it due to lack of gadgets measuring it.

Conclusion:

Based on the present study, we conclude that dexmedetomidine in a dose of 1µg/kg as pre operative infusion in patients undergoing lapararoscopic surgeries gives better haemodynamic stability, post operative analgesia, sedation and reduction in the dose of inhalational anesthetic agent compared to 0.7µg/kg dose without increase in the incidence of adverse effects. Dexmedetomidine upto dose of 1µg/kg produces light sedation which does not affect maintenance of airway.

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