ECRONICON OPEN ACCESS

EC PHARMACOLOGY AND TOXICOLOGY

Research Article

Impact of Intraoperative Low Dose Dexmedetomidine Infusion on Perioperative Hemodynamics and Analgesia in Laparoscopic Surgeries Under General Anaesthesia: A Randomized Control Trial

Sapna Jain[1], Smriti Sinha[2]*, Reena R Kadni[3] and R Shekhar[3]

[1]*Department of Intensive Care, Columbia Asia Hospital, Whitefield, Bangalore, India*

[2]*Department of Anaesthesia and Critical Care, Manipal Academy of Higher Education/Manipal Tata Medical College, India*

[3]*Department of Anaesthesia, Bangalore Baptist Hospital, Bangalore, India*

***Corresponding Author:** Smriti Sinha, Department of Anaesthesia and Critical Care, Manipal Academy of Higher Education/Manipal Tata Medical College, India.

Received: March 02, 2021; **Published:** May 28, 2021

Abstract

Background: Laparoscopic surgeries are minimally invasive surgery which needs creation of pneumoperitoneum and specific positions to facilitate surgery. It leads to hemodynamic changes intraoperatively and mandates pharmacological intervention to manage that. Dexmedetomidine is selective alpha agonist which helps in blunting hemodynamic stress response and have supplemental analgesic effect.

Aims: The current randomized control trial used infusion of lower doses of Dexmedetomidine intraoperatively to evaluate its effect on the blunting of stress response of intubation and creation of pneumo-peritoneum. The additional analgesic role of Dexmedetomidine was also assessed.

Methodology: Total 80 patients were recruited in the study, which were randomly allocated in two groups. Forty patients were included in the group D, who received Dexmedetomidine in dose of 1 μ/kg/min over 10 min followed by 0.2 μ/kg/hr till the end of the surgery. In placebo group (group P), volume adjusted infusion of sterile saline continued with same time limits. The hemodynamic effects at intubation, pneumoperitoneum creation and analgesic requirement in postoperative time were noted.

Results: The vitals were more stable in Dexmedetomidine group, compared to placebo group, after intubation, pneumoperitoneum creation and postoperatively with $p < 0.05$. The need of induction agent was 32% lower in group D and to maintain hemodynamics during pneumoperitoneum 44% higher MAC was required in placebo group. There was a highly significant difference between the two groups in sedation score at the initial 10 min bolus infusion, immediate post op 10 min and pain score in the immediate post op 10 min ($P < 0.001$).

Conclusion: The infusion of Dexmedetomidine effectively blunts the hemodynamic stress response of intubation and pneumoperitoneum with additional advantage of reduced postoperative requirement of analgesics.

Keywords: *Dexmedetomidine; Intubation Stress Response; Laparoscopic Surgery; Pneumoperitoneum; Analgesic Efficacy*

Introduction

Laparoscopic surgeries are a type of minimally invasive surgeries which needs small abdominal incision to access the abdominal organs. To provide better access and visibility to surgeons, these procedures need pneumoperitoneum creation and present challenges due

to increased intra-abdominal pressure. The changes in physiology of cardiovascular, respiratory, renal and splanchnic system are proportional to increase in abdominal pressure. The various patient positions and carbon-dioxide, which is commonly used gas for insufflation, further adds to hemodynamic changes, hypercarbia, rise in end tidal carbon dioxide, altered acid base balance, sympathetic nervous system stimulation and initiates stress response [1-3]. Various pharmacological agents have been used to prevent hemodynamic changes associated with pneumoperitoneum.

Dexmedetomidine is highly selective α_2 receptor agonist with affinity ration of α_2/α_1 (1620:1). The α_2 agonistic activity leads to conscious sedation, analgesic activity, sympatholytic, cardiovascular stabilizing effect and prevents emergence agitation at extubation with less unwanted cardiovascular effects from α_1 receptor activation [4-7]. Dexmedetomidine evokes a biphasic blood pressure response. At lower doses the dominant action is sympatholysis which are mediated by alpha 2 A adrenergic receptor. At the higher doses the hypertensive action dominates via the activation of alpha 2 B adrenoreceptors [5].

In previous studies, dexmedetomidine infusion have been used in various rates ranging from 0.1 to 10 µ/kg/hr. The studies with higher infusion rates had high incidence of adverse effects like hypotension and bradycardia [8].

Aim of the Study

The present study has been undertaken to evaluate the effects of lower dose of dexmedetomidine intravenous infusion (1 µ/kg over 10 min followed by 0.2 µ/kg/hr) in preventing hemodynamic response to laryngoscopy, intubation, with carbon dioxide pneumoperitoneum and observe any other effects.

Materials and Methodology

The current study was conducted after Institutional Ethics Committee approval in a tertiary care center. The study included patients of both gender, in age group of 18 - 65 years, in American Society of Anaesthesiology grade 1 and 2, who were electively posted for laparoscopic abdominal surgeries. The laparoscopic surgeries which got converted to laparotomy were excluded from the study. Pregnant patients, patients with history of drug allergy and hypertensive patients who were on alpha 2 agonists, alpha-methyl dopa and beta blockers, were excluded too. During pre-operative evaluation written and informed consent were taken from the patients who satisfied the inclusion criteria. Patients were kept nil per orally for 6 hours for solids and 2 hours for liquids before surgery and aspiration prophylaxis was given to all the patients in form of intravenous ranitidine 50 mg and metoclopramide 10 mg one hour before surgery.

Patients were divided into study (group D) and placebo (group P) groups by block randomization with unequal number of block. The group D received Dexmedetomidine 1 µ/kg intravenously over 10 minutes as a bolus dose and then at the rate of 0.2 µ/kg/hour. The placebo group received volume adjusted normal saline. The infusion drugs were prepared by anaesthesiologist not involved in the procedure and assessment of patients. The infusion in both the groups were continued till the removal of laparoscopic ports.

The sample size was estimated based on expected outcome of previous study [7] using EpiInfo software. It was decided to have sample size of 80 patients, with 40 participants in both the groups, considering risk/prevalence ration of 1.3 and risk/prevalence difference of 20.

In operation theater, baseline vitals including heat rate (HR), noninvasive blood pressure (NIBP) including systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MAP) with oxygen saturation (SpO_2) were recorded. Two separate intravenous (IV) access were secured, one for regular fluid and other dedicated to test drug administration. After Fluid loading of 5 ml/kg and bolus infusion of test drug, sedation was checked based on Ramsay sedation scale [8]. The patients were preoxygenated for 3 minutes, followed by IV fentanyl 2 µg/kg and 0.2 mg glycopyrrolate. Induction of anaesthesia was done with graded dose of propofol upto 2 mg/kg, keeping loss of verbal response as end point, followed by check ventilation and atracurium 0.5 mg/kg IV. The airway was secured by endotracheal intubation after which end tidal CO_2 ($EtCO_2$) monitoring was started. For maintenance of anaesthesia oxygen and air

(50:50) with 1 - 2% isoflurane was used with MAC monitoring. The test drug infusion continued throughout the surgery till laparoscopic port removal. The $EtCO_2$ was maintained between 30 to 40 mmHg by adjusting minute ventilation during pneumoperitoneum. The intra-abdominal pressure was maintained between 12 - 14 mm Hg. Hypotension (MAP < 60 mmHg) was treated with intravenous injection of ephedrine 6 mg and intravenous fluids. Hypertension (more than 20% from baseline) was treated first with titrated inhalational agent with MAC monitoring and later by 50 µg of fentanyl, if needed. Bradycardia (heart rate < 50 bpm) was treated with intravenous injection of atropine 0.6 mg. Paracetamol 1 gm IV was given intraoperatively and local anaesthetic infiltration at port site was done for analgesia. At the end of surgery, intravenous ondansetron 0.1mg/kg was given and residual neuromuscular block was reversed with injection neostigmine 0.05mg/kg and injection glycopyrolate 0.01 mg/kg. Patients were extubated and transferred to the Post Anaesthesia Care Unit (PACU) for monitoring.

All the vitals including SBP, DBP, MAP, HR, SpO_2 and $EtCO_2$ (after intubation) were recorded throughout the surgery. The dose of induction agent, MAC (Minimum alveolar concentration of inhalational agent) during pneumoperitoneum and added doses of fentanyl were noted. In the PACU; SBP, DBP, MAP, HR, SpO_2 and sedation score were recorded for one hour. Pain was assessed using Visual Analogue Scale (0 = no pain, 10 = worst pain) [10]. VAS ≥ 4 was treated with slow 50 µg fentanyl. The requirement of fentanyl was noted till 6 hours postoperatively. Undesirable effects (nausea, vomiting, bradycardia, hypotension, respiratory depression, shivering, sedation) either complained of or observed during the course of the study up-to one hour into postoperative period were also recorded.

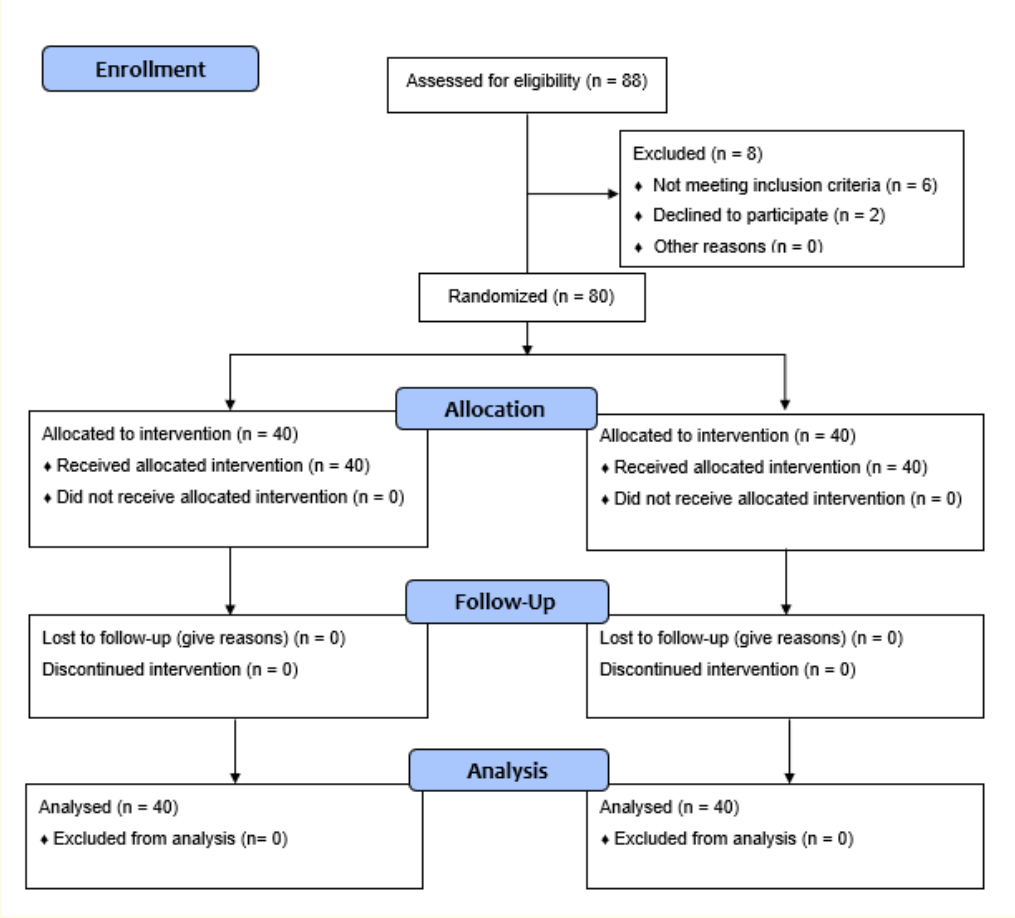


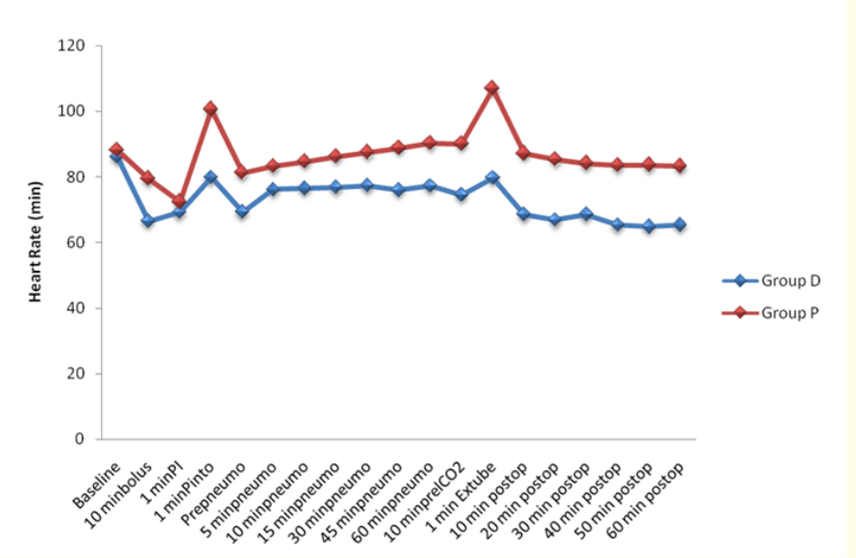
Figure 1: *CONSORT flow diagram.*

Results

The two group of patients were comparable in age, gender, ASA grade and weight (Table 1). There was no difference between the two groups in baseline HR, SBP, DBP and MAP. The HR decreased from the baseline value of 86.08 ± 13.87 to 66.55 ± 13.59 at the end of 10 minute bolus infusion in patients who received dexmedetomidine which was a significant decrease ($p < 0.001$). Out of 40 patients, 2 (5%) developed bradycardia in dexmedetomidine group following bolus infusion, requiring pharmacologic intervention. Immediately after intubation at 1 min, there was 8% fall in HR in dexmedetomidine group compared to 13% increase in HR in placebo group (Graph 1). After 15 min and 30 min of pneumoperitoneum there was a significant difference in HR between the two groups ($P < 0.001$) and remained significantly lower in the dexmedetomidine group throughout the pneumoperitoneum and in PACU compared to placebo group.

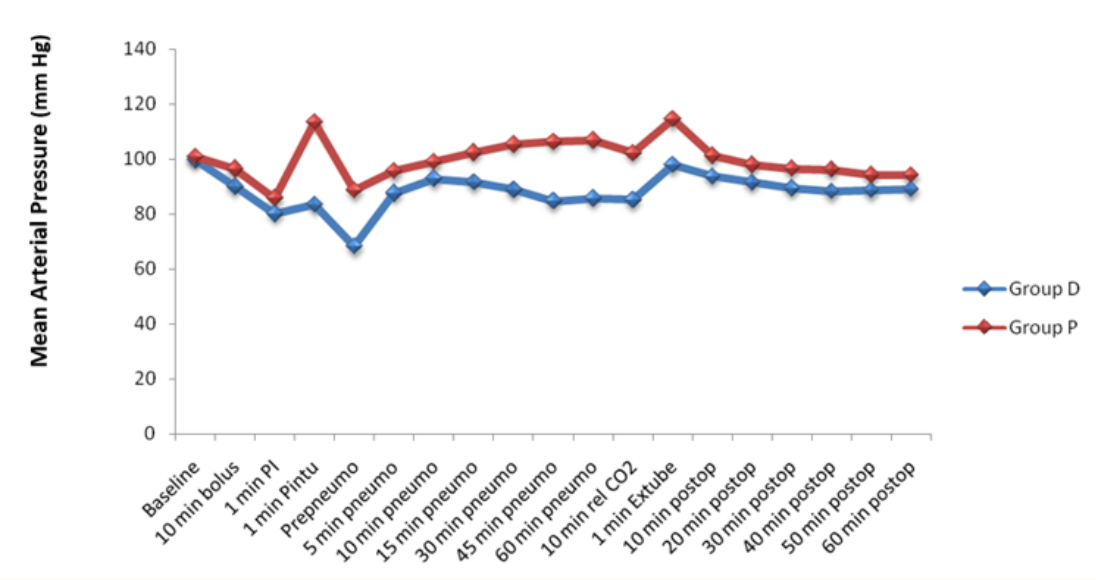
Age in years	Group D (n = 40)		Group P (n = 40)		
	No	%	No	%	P value
20 - 30	6	15.0	3	7.5	0.65
31 - 40	13	32.5	16	40.0	
41 - 50	10	25.0	16	40.0	
51 - 60	9	22.5	5	12.5	
> 60	2	5.0	0	0.0	
Mean ± SD	42.85 ± 11.37		41.88 ± 7.36		
Gender					
Male	13 (32.5%)		18 (45%)		0.359
Female	27 (67.5%)		22 (55%)		
ASA Grade					
Grade 1	20 (50%)		24 (60%)		0.50
Grade 2	20 (50%)		16 (40%)		
Weight (kg)					
41 - 50	5 (12.5%)		6 (15%)		0.627
51 - 60	14 (35%)		19 (47.5%)		
61 - 70	18 (45%)		11 (27.5%)		
71 - 80	3 (7.5%)		4 (10%)		
Mean ± SD	60.58 ± 7.26		59.78 ± 7.40		

Table 1: *Comparison of basic characteristics of the two groups of patients studied.*



Graph 1: *Heart rate of the patients studied.*

At all points of time the SBP, DBP and MAP were lower in dexmedetomidine group compared to placebo group (Graph 2). The MAP varied from 99.70 ± 11.80 to 68.08 ± 11.51 in dexmedetomidine group and from 114.43 ± 7.94 to 85.7 ± 8.11 in placebo group. In dexmedetomidine group, the MAP value following intubation at 1 min, decreased by 15% from the baseline, whereas in placebo group it increased by 13% from baseline value. At 30 min of pneumoperitoneum the MAP value in dexmedetomidine group was 88.73 ± 11.37 compared to 105.35 ± 10.08 in placebo group and it remained low throughout pneumoperitoneum and in PACU, which was statically significant.



Graph 2: *Comparison of MAP between group D and P.*

The average dose of induction agent (propofol) in group D was 78mg while in group P it was 116 mg. The need of propofol was 43% more in placebo group. The MAC needed to maintain hemodynamics among placebo group was approximately 1.5 MAC, while 0.9 MAC was sufficient in group D. None of the patient needed any intraoperative fentanyl bolus dose.

There was a highly significant difference between the two groups in sedation score particularly after the initial 10 min bolus infusion and immediate post op 10 min (Table 2). There was a significant difference between the two groups in pain score in the immediate post op 10 min ($P < 0.001$), thereafter the pain scores were comparable between the two groups.

	Sedation score			Pain score (VAS)		
	Group D	**Group P**	**P value**	**Group D**	**Group P**	**P value**
10 min bolus	2.98 ± 0.73	2.15 ± 0.36	<0.001			
10 min postop	3.03 ± 0.66	2.48 ± 0.82	0.001	1.58 ± 2.11	3.23 ± 2.01	0.001
20 min postop	2.83 ± 0.68	2.60 ± 0.63	0.128	1.85 ± 2.25	2.38 ± 1.43	0.216
30 min postop	2.83 ± 0.55	2.55 ± 0.55	0.028	1.65 ± 1.63	2.08 ± 1.00	0.163
40 min postop	2.70 ± 0.46	2.45 ± 0.55	0.031	1.87 ± 1.24	2.08 ± 0.86	0.405
50 min postop	2.63 ± 0.49	2.43 ± 0.55	0.090	1.77 ± 0.92	2.08 ± 0.80	0.123
60 min postop	2.58 ± 0.50	2.38 ± 0.49	0.075	1.75 ± 0.84	2.05 ± 0.78	0.102

Table 2: *Sedation and pain score in two groups of patients studied.*

In dexmedetomidine group (Table 3), 2.5% of the patients had postop shivering and 5% of the patients had PONV. In placebo, 10% of the patients had postop shivering, and 7.5% of the patients had PONV. In the postop period, 22% of the patients in dexmedetomidine group required fentanyl compared to 40% of the patients in placebo group.

Complications	Group D (n = 40)		Group P (n = 40)	
	No	%	No	%
Hypotension	-	-	-	-
Bradycardia	-	-	-	-
Shivering	1	2.5	4	10
Hypoxia	-	-	-	-
PONV	2	5	3	7.5
Amount of Fentanyl used (µg)				
≤ 50 µg	7	17.5	10	25
50 - 100 µg	2	5	5	12.5
> 100 µg	-	-	1	2.5

Table 3: *Postoperative events and amount of Fentanyl used in two groups of patients studied.*

Discussion

Stress response of intubation and hemodynamic response of pneumoperitoneum

In current study, after 10 minute of 1 µg/kg dexmedetomidine infusion, heart rate was lower compared to placebo group and stress response of intubation was also effectively blunted. The presynaptic activation of the α_2 adrenoceptor inhibits the release of norepinephrine and postsynaptic activation of α_2 adrenoceptors in the central nervous system inhibits sympathetic activity and leads to decrease in blood pressure and HR [11]. Pneumoperitoneum required for laparoscopy results in an increase in arterial pressure, systemic and pulmonary vascular resistance early after the beginning of intra-abdominal insufflation. Both mechanical and neurohumoral factors contribute to these hemodynamic changes. Interestingly alpha 2 adrenergic agonists have been shown to improve hemodynamic stability during laparoscopy. Dexmedetomidine, by its sympatholytic effect decreases mean arterial pressure and heart rate by reducing norepinephrine release [12].

At one min post induction there was no difference in mean heart rate between the two groups probably because of the effect of inj glycopyrrolate. At 1 min after intubation, there was decrease in HR in dexmedetomidine group while in placebo group because of intubation stress response there was increase in HR, in spite of maintaining 1.3 MAC on monitor. Similar findings were observed in other studies [13-15]. Twenty five percent of the patients in dexmedetomidine group had significant hypotension in pre-pneumoperitoneum period, which recovered after fluid boluses and Inj Ephedrine 6 mg IV. The other vitals like SBP, DBP and MAP were lesser in dexmedetomidine group than placebo group after bolus dose of test drug and the same trend maintained at all points of time during pneumoperitoneum, post extubation and in PACU as well.

Dexmedetomidine have been used intraoperatively in various doses 0.1 - 10 µg/kg/hr for stable hemodynamics. A study conducted by Sağıroğlu., *et al*. [16] concluded that the intubation response was better prevented with 1 µg/kg Dexmedetomidine dose compared to lower doses, similar finding was obtained in current study. Dexmedetomidine is an effective drug to blunt the intubation response after ten minutes of infusion at rate of 1 µ/kg/min [13,14]. The stress response of intubation and hemodynamic changes of pneumoperitoneum creation and position change in laparoscopic surgeries can be well controlled by higher doses but chances of bradycardia will be there. In

current study, with lower maintenance infusion dose of 0.2 µg/kg/hr the same advantageous effects of sympatholysis could be achieved without any side effects.

Anaesthetic adjuvant action

Dexmedetomidine is an anesthetic adjuvant that decreases requirement of anesthetics. The requirement of induction agent and inhalational agents were found to be markedly reduced, which was in accordance to previous done studies [17].

Sedation score

The sedative effect of Dexmedetomidine is due to its stimulation of α_2 A subtype located in locus coeruleus [18]. In the present study, sedation score was highly significant between the two groups after the 10 min bolus infusion and in immediate postop 10 min. The patients in dexmedetomidine group were asleep but arousable in the immediate postop period, gradually over the next 20 - 60 min they were awake and comfortable. The previous studies [16,19] also showed that the dexmedetomidine infusion resulted in significant arousable sedation, while oxygen saturation, $EtCO_2$, and respiratory rate were well preserved throughout the infusion and recovery period.

Analgesic requirement

Dexmedetomidine has analgesic effects and is a potential non-opioid adjuvant to improve analgesia which helps in decreasing the number of opioid-associated adverse events [12,20]. In current study, the mean pain score in dexmedetomidine group at 10 min postoperative period was 1.58 ± 2.11 compared to 3.23 ± 2.01 in placebo group which was significantly low. However, over the next 20 - 60 min post-operative period the pain score between the two groups were comparable. The total amount of rescue fentanyl administered in PACU in dexmedetomidine group was 530 mcg compared to 960 mcg in placebo group. 22% of the patients in dexmedetomidine group required rescue fentanyl compared to 40% patients in placebo group.

Other effect

PONV is a common complication for patients undergoing laparoscopic surgery, regardless of the anaesthetic technique used. In current study the recovery area, 2 patients in dexmedetomidine group and 3 patients in placebo group had nausea and vomiting. One patient in dexmedetomidine group and 4 patients in placebo group had shivering.

Conclusion

Dexmedetomidine 1 µg/kg bolus dose followed by low maintenance dose of 0.2 µg/kg/hr effectively attenuates the vasopressor response to laryngoscopy and intubation and the sympathoadrenal response occurring with pneumoperitoneum. Dexmedetomidine produces arousable sedation without producing significant respiratory depression. It also reduces opioid analgesic requirement during postop period.

Bibliography

1. Joshi GP. "Anesthesia for laparoscopic surgery". *The Canadian Journal of Anesthesia* 49 (2002): R45-R49.

2. Das M., *et al*. "Haemodynamic changes during laparoscopic cholecystectomy: Effect of clonidine premedication". *Indian Journal of Anaesthesia* 51.3 (2007): 205-210.

3. Sood J and Kumar VP. "Anaesthesia for laparoscopic surgery". *Indian Journal of Surgery* 65.3 (2003): 232-240.

4. Hall JE., *et al*. "Sedative, Amnestic, and Analgesic Properties of Small-Dose Dexmedetomidine Infusions". *Anesthesia and Analgesia* 90 (2000): 699-705.

5. Kamibayashi T., *et al*. "Clinical Uses of alpha 2 Adrenergic Agonists". *Anaesthesiology* 93.5 (2000): 1345-1349.

6. Murthy TVPS and Singh R. "Alpha 2 Adrenoceptor Agonist – Dexmedetomidine Role in Anaesthesia and Intensive Care: A Clinical Review". *Journal of Anaesthesiology Clinical Pharmacology* 25.3 (2009): 267-272.

7. Carollo DS., *et al*. "Dexmedetomidine: A Review of Clinical Applications". *Current Opinion in Anesthesiology* 21.4 (2008): 457-461.

8. Vora KS., *et al*. "The effects of dexmedetomidine on attenuation of hemodynamic changes and there effects as adjuvant in anaesthesia during laparoscopic surgeries". *Saudi Journal of Anaesthesia* 9.4 (2015): 386-392.

9. Ramsay MA., *et al*. "Controlled sedation with alphaxolone-alphadalone". *British Medical Journal* 2 (1974): 656-659.

10. Delgado DA., *et al*. "Validation of Digital Visual Analog Scale Pain Scoring With a Traditional Paper-based Visual Analog Scale in Adults". *Journal of the American Academy of Orthopaedic Surgeons* 2.3 (2018): 1-6.

11. Gertler R., *et al*. "Dexmedetomidine:a novel sedative-analgesic agent". *Proc* 14.1 (2001): 13-21.

12. Tufanogullari B., *et al*. "Dexmedetomidine infusion during laparoscopic bariatric surgery: The effect on recovery outcome variables". *Anaesthesia and Analgesia* 106.6 (2008): 1741-1748.

13. Menda F., *et al*. "Dexmedetomidine as an adjunct to anaesthetic induction to attenuate hemodynamic response to endotracheal intubation in patients undergoing fast track CABG". *Annals of Cardiac Anaesthesia* 13.1 (2010): 16-21.

14. Bhattacharjee DP., *et al*. "Effect of Dexmedetomidine on hemodynamics in patients undergoing Laparoscopic Cholecystectomy- A Comparative Study". *The Journal of Clinical Pharmacology* 26.1 (2010): 45-48.

15. Talke P., *et al*. "Postoperative Pharmacokinetics and sympatholytic effects of dexmedetomidine". *Anesthesia and Analgesia* 85 (1997): 1136-1142.

16. Sağıroğlu AE., *et al*. "Different doses of dexmedetomidine on controlling haemodynamic responses to tracheal intubation". *The Internet Journal of Anesthesiology* 27 (2010): 2.

17. Ghodki PS., *et al*. "Dexmedetomidine as an anaesthetic adjunct in laparoscopic surgery: An observational study using entropy monitoring". *Journal of Anaesthesiology Clinical Pharmacology* 28.3 (2012): 334-338.

18. Hunter JC., *et al*. "Assessment of the role of alpha 2 adrenoceptor subtypes in the antinociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice". *British Journal of Pharmacology* 122 (1997): 1339-1344.

19. Laha A., *et al*. "Attenuation of sympathoadrenal responses and anaesthetic requirement by dexmedetomidine". *Anesthesia, Essays and Researches* 7.1 (2013): 65-70.

20. Bielka K., *et al*. "Dexmedetomidine infusion as an analgesic adjuvant during laparoscopic cholecystectomy: a randomized controlled study". *BMC Anesthesiology* 18 (2018): 44.

Volume 9 Issue 6 June 2021