Effects of preoperative single bolus dose of dexmedetomidine on perioperative hemodynamics in elective laparoscopic cholecystectomy

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Abstract

Minimal surgical access techniques have become a gold standard of patient care in present era, laparoscopic cholecystectomy is preffered treatment of choice for gall stones. Along with advantages, it is also associated with severe sympathoadrenal stress response, a cause for morbidity and mortality. Dexmedetomidine is an highly selective alpha2 adrenoceptor (α2-AR) agonist, seems to control this sympathetic response and provide a stable perioperative haemodynamics.

Aim of the Study: To investigate effects of preoperative single bolus dose of Dexmedetomidine on hemodynamic parameters in patients posted for Elective Laparoscopic Cholecystectomy.

Design: Randomised Prospective Double-Blind Study.

Materials and Methods: 50 ASA Gr I & II patients belonging to both sex in age group of 20 to 50yrs scheduled for Elective Laparoscopic Cholecystectomy were randomly divided into two groups of 25 each Group-D (Dexmedetomidine) and Group – S (Placebo (0.9% Saline)) A Balanced General Anaesthesia technique included Propofol, Vecuronium IPPV & Isoflurane 0.5%. Perioperatively SBP, DBP, MAP, HR were recorded at predetermined intervals - Pre-op, After Induction, After Intubation & 15 mins interval and extubation data was analysed statistically.

Results: In Group D - HR, MAP, SBP, DBP were significantly less in comparision to Group S.

Conclusion: A single bolus dose of Dexmedetomidine preoperatively effectively attenuates sympathoadrenal stress responses to laparoscopy results in stable perioperative hemodynamics.

Keywords: CO_2 insufflation, Stress response, Dexmedetomidine, α_2- adrenoceptor agonist.

Introduction

The use of laparoscopic technique in general surgery has gained increasing popularity and success of laparoscopic surgery is related to small limited incisions shorter hospital stay, faster recovery and reduced health costs.[1] However, laparoscopic surgery produces significant sympathetic responses, which occur due to anaesthesia and CO_2 insufflation, present a challenging situation. Induction of anaesthesia refers to transition from an awake to an anaesthetized state and induction is a time of physiological disruption with multi-system effects. Laryngoscopy, tracheal intubation and extubation are critical events which trigger severe sympathetic stimulation, in addition to peritoneal CO_2 insufflation. Inadequate control of stress response during perioperative period may result in morbidity and delay speedy functional recovery of patient. An optimal control of sympathetic response is a challenging task for practicing anaesthesiologist.[1,2]

Modern anaesthesia practices plan to attenuate sympathoadrenal response. Use of agents like opioids, propofol, benzodiazepines, β-blockers, calcium channel blockers and vasodilators had variable success.[3]

In recent years, use of α2 agonists in anaesthesia practice is increasing because of anxiolytic, sympatholytic, sedation, anesthetic and analgesic sparing properties. Dexmedetomidine, a highly selective α - AR agonist having sedative and analgesic properties seems to be apt enough to control this sympathetic responses perioperatively[5-7] The aim of study is to investigate effects of pre-operative single dose of Dexmedetomidine @ 1 mcg/kg/min on perioperative hemodynamics in elective laparoscopic cholecystectomy.

Materials and Methods

The present study was undertaken during 2011-2014 at Osmania General Hospital, Hyderabad, to study effects of dexmedetomidine on perioperative hemodynamics in elective laproscopic cholecystectomy. The study had institunional ethics committee approval and written informed consent was obtained from all the patients participated in the study. The study population included 50 randomized, double blinded adult patients in the age group of 20 to 50yrs of both sex belonging to ASA physical status I and II. The study population were randomized into Group D (n=25)- Dexmedetomidine, Group S (n=25) - 0.9% Saline. All the patients were thoroughly investigated and were explained about procedure. On day of surgery, anaesthesia and resuscitation equipment were checked and kept ready. On arrival of patient into operating room ECG, NIBP, Pulse Oximetry were attached and a base line vital signs (HR, MAP & SpO2) were recorded, i.v. line was secured on left forearm with 18G venflon and preloading done with 5 ml/kg of crystalloids. Before induction patients in group D received i.v. dexmedetomidine @1 mcg/kg in 50ml saline as a single dose slow infusion over 10mins, patients in group S received 50ml of 0.9% NS. A Balanced general anesthesia technique was adopted for all patients, glycopyrrolate 0.2mg, fentanyl 2 μg/kg, ondansetron 4 mg,

rantidine 50mg were given i.v. pre-medication. Induction with Propofol @ 2mg/kg, intubation facilitated by 0.1mg /kg vecuronium bromide i.v. and airway secured with appropriate size cuffed orotracheal tube. Pneumoperitoneum created by intraperitoneal CO2 insufflation @ 2ltrs/min and intra-abdominal pressure (IAP) maintained between 10-14mmHg through out surgery. Anaesthesia maintained with IPPV, N_2O:O_2- 50: 50, Isoflurane-0.5%, Circle system with CO_2 absorber and vecuronium for muscle relaxation Intraoperatively $EtCO_2$ was maintained between 35 - 40mmHg. Patients were observed for any adverse events perioperatively. NTG, Nitroglycerine, Labetolol and Metoprolol were kept as rescue drugs to control blood pressure (if MAP exceeds 20% from baseline). Atropine 0.6mg to treat Bradycardia HR < 50 /min and vasopressors - mephentermine and noradrenaline used to treat untoward Hypotension. Intraoperatively - HR, noninvasive BP (SBP, MAP, DBP)and SpO_2 were measured at pre-determined intervals in both groups : Baseline, after induction, after intubation, 15 min, 30 min, 45 min, 60 min of PNP, Extubation and at 1st hr postoperatively. At end of surgery neuromuscular blockade reversed with neostigmine 60 µg and glycopyrrolate 10 µg/kg and after meeting extubation criteria, trachea extubated and patients were transferred to recovery room and monitored for hemodynamics, analgesia, sedation and postoperative side effects. The results were entered in a data sheet and analysed. Mean ± S.D. were calculated for all quantitative variables.

Postoperative pain intensity was assessed using a 10 point visual analogue scale (VAS), 0- no pain & 10-worst pain imaginable. VAS >3 -- Tramadol 100 mg i.v. and ondansetron 4 mg i.v. as antiemetic, degree of sedation assessed using 6 point Ramsay sedation scale and sedation score of > 3 was considered as undue sedation:

Exclusion Criteria

1. Patients posted for emergency surgical procedures
2. Patients with cardiovascular or respiratory, renal disorders,
3. Obesity, Diabetes, Hypertension
4. Anticipated difficult airway
5. Pregnancy & Breast feeding women
6. History of sleep apnea
7. Psychiatric disorder
8. Pre-op Hypotension
9. Surgeries converted to open cholecystectomy

Observations and Results

Statistical analysis of the results data done using SPSS statistical software Mean, SD and "p" values were comparision of clonidine and dexmedetomidine calculated. Comparision between two groups at a time (inter group comparision) was done using Student's unpaired't' test. p <0.05 was considered statistically significant, p<0.01 highly significant, p>0.05- insignificant.

Out of the 50 patients included in the study 25 were female and 25 were male. The average age in the group D is 40.5yrs (±11.5) and Group S (42.96±9.3), average weight in group D - 55.24±10.16 and in group S -56.34 ± 9.5 (Table 1). There results with respect to age, sex, weight and ASA physical status were comparable and had no stastical significance.

Table 1: Demographic profile of patients

	Group D	**Group S**	**'p' value**
	Mean± S.D.	Mean±S.D.	
Age (in yrs)	40.5±11.5	42.96±9.3	0.4 (NS)
Sex (M/F)	13/12	12/13	
Weight(in kgs)	55.24±10.16	56.34 ±9.5	0.6(NS)

Table 2: Changes in heart rate (HR)

	Changes in Heart rate		***p***'value
	Group D	**Group S**	
	Mean± S.D.	Mean ± S.D.	
Pre-op	81.17 ±10.80	83.68 ± 8.37	0.30
After Induction	69.71 ± 7.96	78.24 ± 11.51	<0.01(HS)
After Intubation	76.54 ± 7.80	96.76 ± 8.84	<0.01(HS)
15min after PNP	75.17 ± 8.98	94.73 ± 11.43	<0.01(HS)
30min after PNP	76.54 ± 8.70	91.72 ± 6.41	<0.01(HS)
45min after PNP	76.33 ± 8.35	94.60 ± 7.47	<0.01(HS)
60min after PNP	76.63 ± 6.61	92.84 ± 8.06	<0.01(HS)
Extubation	84.67 ± 8.66	93.08 ± 10.14	<0.01(HS)
Post-op 1hr	90.44 ± 6.55	88.17 ± 8.55	0.40

(PNP – Pneumoperitoneum)

Table 3: Changes in systolic blood pressure (SBP).

	Changes in Systolic Blood pressure		'*p*' value
	Group **D**	Group **S**	
	Mean ± S.D.	Mean ± S.D.	
Pre-op	130.00 ± 5.62	134.60 ± 8.24	0.06
After Induction	98.19 ± 6.68	117.00 ± 6.55	0.01(S)
After Intubation	121.46 ± 6.53	130.80 ± 5.46	< 0.01(HS)
15min after PNP	121.92 ± 3.57	132.08 ± 4.24	0.01(S)
30min after PNP	124.81 ± 3.38	128.04 ± 3.27	0.01(S)
45min after PNP	122.65 ± 4.52	129.08 ± 4.27	< 0.01(HS)
60min after PNP	122.31 ± 4.56	124.23 ± 2.63	0.05
Extubation	132.00 ± 3.94	134.08 ± 4.18	0.01(S)
Post-op1 hr	123.38 ± 5.43	122.80 ± 3.08	0.68

(PNP-pneumoperitoneum)

Table 4: Changes in diastolic blood pressure (DBP)

	Changes in Diastolic Blood Pressure		'*p*' value
	Group D	**Group S**	
	Mean±S.D.	Mean± S.D.	
Pre-op	83.08 ± 8.53	89.92 ± 6.85	0.08
After Induction	55.00 ± 8.52	80.81 ± 7.74	<0.01(HS)
After Intubation	74.35 ± 7.31	83.81 ± 5.58	0.01(S)
15min after PNP	76.12 ± 7.79	86.77 ± 5.09	< 0.01(HS)
30min after PNP	75.96 ± 9.23	84.96 ± 5.75	< 0.01(HS)
45min after PNP	74.00 ± 8.00	84.23 ± 5.35	< 0.01(HS)
60min after PNP	71.00 ± 11.46	81.00 ± 6.51	< 0.01(HS)
Extubation	74.00 ± 6.81	93.88 ± 8.91	0.01(S)
Post-op 1hr	90.44 ± 7.49	75.77 ± 9.11	0.74

(PNP- Pneumoperitoneum)

Table 5: Changes in mean arterial pressure, MAP

	Changes in mean arterial pressure		'*p*' value
	Group D	**Group S**	
	Mean± S.D.	Mean ± S.D.	
Pre-op	99.42±7.01	99.48±8.16	0.16
After Induction	65.17±7.48	92.68±6.56	< 0.01 (HS)
After Intubation	89.79±5.39	99.56±5.08	< 0.01(HS)
15min after PNP	92.13±5.57	101.32±4.02	< 0.01(HS)
30min after PNP	92.17±6.84	99.60±4.19	< 0.01(HS)
45min after PNP	86.50±7.64	99.36±4.50	< 0.01(HS)
60min after PNP	87.30±7.94	95.56±4.87	< 0.01(HS)
Extubation	90.79±5.63	107.04±6.59	< 0.01(HS)
Post-op 1hr	91.44±6.56	90.79±6.74	0.06

(Pneumoperitoneum)

Discussion

Laparoscopic surgeries have become gold standard of care for various surgical procedures. Hemodynamic changes with pneumoperitoneum were first recognized in 194.[64] The physiological changes observed during laparoscopic cholecystectomy are a result of general anaesthesia, patient position, pneumoperitoneum PNP), and increased intra-abdominal pressure(IAP).[9] The physiological changes reflect a marked symathoadrenal manifested as hypertension and tachycardia, increased plasma levels of catecholamines (epinephrine, norepinephrine), vasopressin and plasma renin activity[8] increasing systemic and pulmonary vascular resistance, and reduced cardiac output, predispose a vulnerable patient to life threatening myocardial ischemia. Hence, a drug, which can blunt hemodynamic responses to laryngoscopy, intubation and pneumoperitoneum without any adverse effects was needed for purpose of attenuating hemodynamic responses. In recent years, use of α2 agonists is increased due to sympatholytic, anxiolytic, sedative, opioid and analgesic sparing properties.[10] Dexmedetomidine is an imidazole derivative and dextro--rotatory S-enantiomer of racemate medetomidine (50:50) (Kuusela et al. 2001)[11-13]

It is similar to clonidine and highly selective and 8 times more affinity for α_2 adrenocep- -tor (α_2 -AR) and possesses all properties except respiratory depression.[14-16] It produces dose-dependent sedation, anxiolysis and analgesia involving spinal and supraspinal sites (locus ceruleus and dorsal raphe nucleus).[17,18,21] Dexmedetomidine enhances anaesthesia by stimulating central α2 and imidazoline receptors[19 20] and being a more selective α2-agonist has more analgesic properties and its effects mimic stage 2 non-rapid eye movement sleep[22] Its distribution t½ is 6 min (approx.) successfully can be used for attenuating stress response to laryngoscopy.[23] Dexmedetomidine in comparision with conventional sedatives and opiates demonstrated to be associated with reduced delirium and agitation, minimal respiratory depression, and desirable cardiovascular effects.[24-32] Hemodynamic effects are due to central sympatholytic and peripheral vaso- -constrictive effects.[33-35] A biphasic response of blood pressure occurs with a bolus dose,[36] seen more often in young patients[37] it is due to stimulation of α2 B receptors in vascular vascular smooth muscles, reduces serum NEpi by activating receptors in medullary vasomotor center (locus coeruleus), suppressi hemodynamic response to intubation, extubation without any side effects.[38-40] Additional effects result from central stimulation of parasympathetic outflow, perioperatively decreases serum catecholamines by 90%[41] and Table 2. Comparison of dexmedetomidine with other ICU sedatives blunts haemodynamic response to laryngoscopy, tracheal intubation, pneumoperitoneum and extubation.[42-45] Dexmedetomidine exhibits linear pharmacokinetics has rapid distribution phase, used as i.v. infusion up to 24 hours.[46,47] Its short t ½ makes it an ideal drug for intravenous (IV) titration.[48,49] Optimal dose for attenuating pressor response seems to be 1 mcg/kg with lesser doses not being effective.[50,66] Recent studies have found definite role of dexmedetomidine in reducing dose requirement of propofol for induction and maintenance of anaesthesia.[51,52] Dexmedetomidine has no significant effect on response to verbal commands and extubation time (Bhattacharjee*etal).*[53] It has opioid sparing effect and increases time interval to receive first rescue analgesia been found to reduce intra and post-operative opioid requirement.[54-57] In the present study it was noticed from the results that hemodynamics during intraoperattve period were favorable in the dexmedetomidine group both at induction- Group D (MAP-65.17±7.48), Group S (MAP – 92.68±6.56) and intubation Group D (MAP-89.79±5.39), Group S (MAP – 99.56±5.08) and these benefits continued well from creating pneumoperitoneum to extubation and significance proved statistically ($p<0.01$).

Clonidine	Dexmedetomidine
Developed in the 1960s	Developed in the 1980s
Clinically used first as antihypertensive in 1966	Clinically approved as sedative and analgesic used in ICU in 1999
Ratio α 2:α 1 receptor binding is 220:1	Dexmedetomidine is 7-8 times more specific for a2. Ratio α 2:α 1 receptor binding is 1620:1
Clonidine is a partial agonist at the α 2 adrenergic receptor	Dexmedetomidine is a full agonist at the α 2 adrenergic receptor
Octanol/buffer partition coefficient: 0.8	Octanol/buffer partition coefficient: 2.8 more lipophilic (3.5-fold) than clonidine
The maximum reduction in inhalational anesthetic requirement to maintain 1 MAC provided by clonidine is 50%	Dexmedetomidine has been shown to result in approximately a 90% reduction in inhalational anesthetic requirement to maintain 1 MAC
Plasma half-life is T½: 9-12 hours	Plasma half-life T½: 2-2.5 hours
Protein binding: 50%	Protein binding: 94%
Elimination half life is 8 hrs	Elimination half life is 2 hrs
Distribution half life is >10 min	Distribution half life is 5 min

Effects	Dexmedetomidine	Benzodiazepines	Propofol	Opioids	Haloperidol
Sedation	√	√	√	√	√
Analgesia	√			√	
Alleviation of anxiety	√	√			
Cooperative sedation	√				
Facilitation of ventilation during weaning	√				
No respiratory depression	√				√
Control of delirium	√				√
Organ protection	√		√		
Control of stress response	√				
Antishivering agent	√				
Mimicking of natural sleep	√				

Based on data from Pandharipande *et al.*[36]

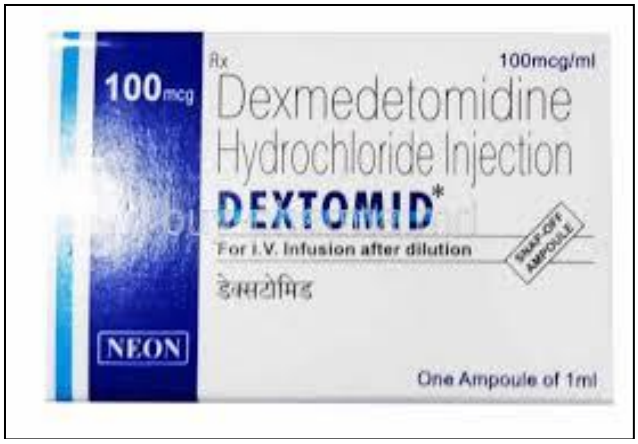

Fig. 1

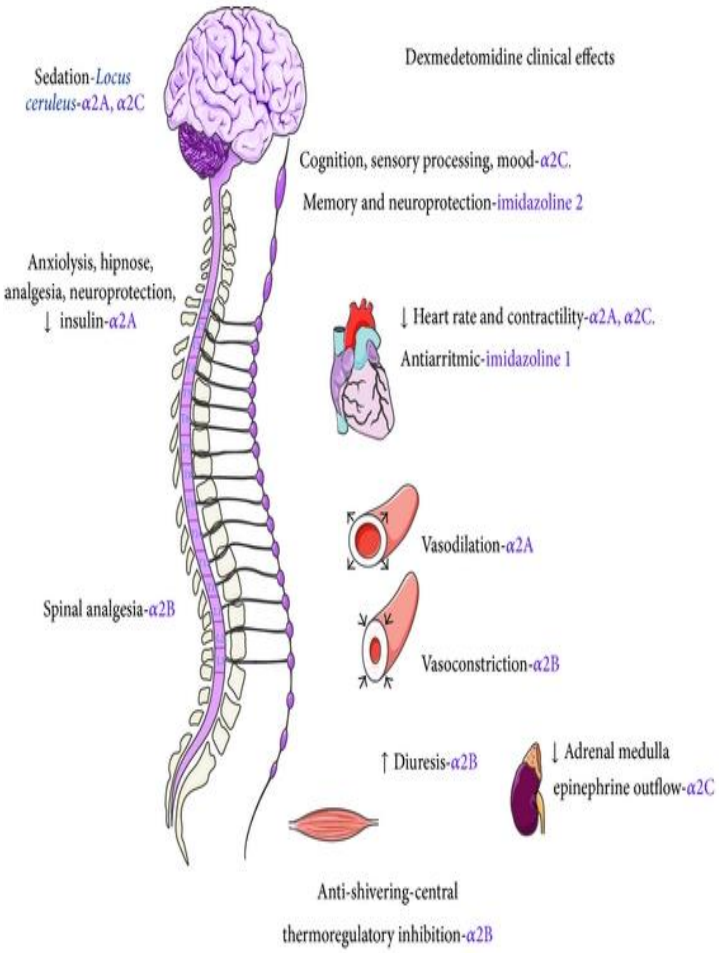

Fig. 2

The hemodynamic and neuroendocrine responses during position changes in laparoscopic cholecystectomy were studied and confirmed by O Leary E, Hubbard K et al,[58] in this study dexmedetomidine effectively attenuated stress response to various critical events in laparoscopic cholesystectomy.

Dexmedetomidine @ 0.2µg/kg/hr infusion perioperatively has maintained significantly lower mean arterial pressure and heart rate. Bhattacharjee et al,[59] correlates with mean arterial pressure and heart rate values in our study, and statistically highly significant($p<0.01$). In our study MAP and HR were significantly lesser after intubation and throughout pneumoperitoneum ($p<0.01$). Yildiz M, Tavlan A, Tuncer S, Reish R et al[60] studied effects of dexmedetomidine on hemodynamic responses to intubation Pre-induction - Fentanyl 1µg/kg resulted in blunting of laryngoscopy responses and reduced naesthetic

requirement our study results were similar to this. HulyaBasar et al [61] studied effects of preanaesthetic dose of dexmedetomidine on induction, hemodynamics and cardiovascular parameters in 40 ASA physical status I and II patients, aged 20 to 60yrs divided into two groups, scheduled for elective cholecystectomy. Group D - 0.5µ/kg dexmedetomidine, roup C- 0.9% Saline. In this study Heart rate and Mean arterial pressure were less in the study group D in comparision to Group C after dexmedetomidine and effect sustained throughout intraoperative period and is statistically significant ($p<0.01$) shows effective attenuation. In our study we have found that rise in MAP and HR due to pneumoperitoneum was effectively blunted. In our study, haemodynamic changes during laryngoscopy, intubation were higher in Group S patients than Group D, suggests dexmedetomidine role in attenuation of hemodynamic response to laryngoscopy.[62] Talke P Li J et al[63] studied effects of perioperative dexmedetomidine infusion @ 1µg/kg in patients undergoing vascular surgery, HR was slower with dexmedetomidine (73±11bpm) than placebo (83±20bpm) which is statistically significant ($p=0.006$) showing stable hemodynamics. Tufanogullari B, White PF, et al[64] studied the effects of demedetomidine infusion on recovery and outcome variables laparascopic bariartric surgery which showed a statistically significant difference in MAP and HR between two groups during perioperative period with favourable outcome. Results of present study were found to be similar. It can be concluded that preoperative single bolus dose of dexmedetomindine effectively attenuates hemodynamic responses to laparoscopic cholecystectomy adds to perioperative hemodynamic stability, smooth extubation and recovery of patients, Sedation produced by dexmedetimidine was acceptable which added to comfort of patient. All patients in Group D were comfortable, conscious, coherent, oriented and pain free.

Conclusion

Dexmedetomidine is a novel sedative analgesic, a preoperative single bolus dose @1µgm/kg effectively blunts sympathoadrenal response to laparoscopic cholecystectomy and maintains perioperative hemodynamic stability. Its effects resemble a near ideal anaesthetic (neuroprotective & cardiovascular stability) and makes it a versatile anaesthesia adjunct to decrease anaesthesia and surgery related morbidity.

Conflict of Interest: None.

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