To Evaluate the Efficacy and Safety of Dexmedetomidine on Hemodynamic Stability in Patients Undergoing Laproscopic Cholecystectomy

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ABSTRACT

Introduction: *Peritoneal insufflation of intra-abdominal pressure >10 mmHg induces a significant alteration of hemodynamics. Use of α-2 adrenergic agonists Dexmedetomidine significantly reduces hemodynamic changes and anesthetic requirements as it has sedative, analgesic, and anxiolytic properties.*

Methods: *100 patients of ASA I- II undergoing laparoscopic cholecystectomy were randomly allocated into two groups of 50 patients each. Group I patients received dexmedetomidine infusion at 0.2µg/kg/hr and Group II patients received normal saline infusion at 0.2µg/kg/h starting after intubation and continued till peritoneal deflation. Parameters noted were pulse rate, mean arterial pressure, oxygen saturation, $EtCO_2$ and isoflurane requirement.*

Results: *In dexmedetomidine group, the haemodynamic response was significantly attenuated. The anaesthetic requirement was also less with dexmedetomidine group without any desaturation.*

Conclusion: *Dexmedetomidine infusion in the dose of 0.2µg/kg/h effectively attenuates haemodynamic stress response to pneumoperitoneum during laparoscopic surgery.*

Key words: *Dexmedetomidine, haemodynamic stress response, laparoscopic cholecystectomy, pmeumoperitoneum.*

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INTRODUCTION

A revolution in laparoscopic surgeries began with laparoscopic cholecystectomy as open surgeries are more painful with higher infection rate.[1]

Laparoscopic technique minimizes trauma and stress response of the interventional procedure. Other advantages include reduced postoperative pain and analgesic requirement, rapid return of gastrointestinal function, shorter hospital stay, and improved postoperative pulmonary function. The operative technique involves insufflations of a gas into the abdominal cavity. An intra-abdominal pressure of 10-15 mmHg is created. Carbondioxide (CO_2) is usually used. Absorption of CO_2 from the peritoneal cavity causes hypercapnia and respiratory acidosis.[2] Inflation pressure can be varied from 0-30mm Hg whereas the total gas flow volume can be set from 0-9.9 L/min.[3]

Both pneumoperitoneum and CO_2 causes adverse cardiovascular effects. Immediately after pneumoperitoneum, plasma level of norepinephrine, epinephrine and plasma renin activity increases. The renin-angiotensin-aldosterone-system is also activated by increased catecholamine level. All these changes contribute to elevated arterial pressure, increased systemic vascular resistance, raised pulmonary artery occlusion pressure and decreased cardiac output. Apart from that, laparoscopic cholecystectomy is performed in reverse Trendelenburg position resulting in reduced preload further reducing cardiac output[4] and mean arterial pressure. These haemodynamic changes gets aggravated specially in elderly and in patients with compromised cardiovascular function.[5]

Various pharmacological agents like nitroglycerine, beta-blockers and opioids are used to provide hemodynamic stability during pneumoperitoneum, but they have their own disadvantages.[6] Remifentanyl, which is rapidly hydrolysed by tissue and nonspecific esterases, provides better control of hemodynamic responses compared with alfentanyl and may therefore be preferable for infusion.[7] α-2 agonists are known to produce analgesia, hypnosis, sedation, sympatholytic effects and attenuate opiod induced muscle rigidity. Recently, the Food and Drug Administration has registered two α-2-adrenergic agonists Clonidine and Dexmedetomidine.[8] The hemodynamic stability provided by clonidine should be helpful in patients with compromised cardiac function, thereby allowing these patients to benefit from all the advantages of laparoscopic approach.[9]

Dexmedetomidine, an imidazole derivative, is a adrenoceptor agonist with high selectivity for α_2-compared with α_1–adrenergic receptors (selectivity

ratio 1620:1 compared with 220:1 for clonidine). It causes a dose-dependent decrease in arterial blood pressure and heart rate associated with a decrease in serum noradrenaline concentration. Dexmedetomidine, in a single pre-anesthetic intravenous dose of up to 0.6µg/kg, has been shown to reduce the requirements for supplementary isoflurane administration during nitrous oxide/oxygen, fentanyl anaesthesia and also lessen the haemodynamic reaction to stressful intra-operative events, while causing few side-effects.[10]

As laparoscopic cholecystectomy is a routinely performed surgery, it is desirable to have a stable intraoperative haemodynamic status. Hence in this study, it has been attempted to study the beneficial effect of α-2 adrenergic agonist dexmedetomidine in maintaining the perioperative parameters during laproscopic cholycystectomy.

MATERIALS AND METHODS

The present study was carried out in 100 patients of ASA Grade I & II between the age group of 20-60yrs of both genders scheduled to undergo elective laparoscopic cholecystectomy. They were randomly divided into two groups of 50 patients each.

Group I (n=50): Dexmedetomidine group-200 mcg (2ml) in 38 ml of 0.9% NS @ 0.2 µg/kg/hr infusion was given.

Group II (n=50): Control group-0.9% saline was given at same rate.

Exclusion criteria:

Patients with chronic hypertension , ASA physical status III , AV block, morbid obesity (>50% above ideal body weight), acute cholecystitis, chronic use of opioid analgesics or β-blockers, asthma or reactive airway disease, menstruation at the time of surgery and those with severe renal, hepatic, endocrine and cardiac dysfunction, was excluded from the study.

A thorough pre-anesthetic evaluation was done a day prior to surgery and all the necessary investigations were carried out including specific investigations if required. A written informed consent was taken from every patient. All the patients were kept fasting overnight and were given tablet alprazolam 0.25 mg and tablet ranitidine 150 mg a night before surgery and at 6 am on the day of surgery.

On arrival to operation theatre, intravenous (IV) line was secured and crystalloid intravenous infusion of 6-8 ml/kg/hr was started. Routine monitoring like ECG, NIBP, pulse oxymetry, capnography was started & baseline parameters were recorded. All patients were premedicated with IV Injection midazolam 1-2 mg and glycopyrolate 0.02 mg/kg. Analgesia was given using nalbuphine 6-8 mg IV 10 minutes prior to induction.

After preoxygenation for 3 minutes with 100% oxygen, general anaesthesia was induced with inj. propofol 2 mg/kg, O_2, N_2O and halothane. Endotracheal intubation was facilitated by muscle relaxant vecuronium bromide 0.1 mg/kg. Group I patients were given dexmedetomidine by IV infusion @ 0.2 µg/kg/hr intraoperatively after tracheal intubation. This drug was prepared in identical 50 ml syringe by adding Dexmedetomidine 200 µg (2ml) in 0.9% saline (38 ml) making a total volume of 40 ml (resulting concentration will be 5 µg/ml).

Group II patients were given 0.9% saline at the same rate. Anesthesia was maintained with O_2: N_2O (50:50), isoflurane, IPPV. Supplemental neuromuscular blockade was achieved with vecuronium bromide. $EtCO_2$ was maintained between 35-40 mmHg.

Pneumoperitoneum was created and Intra-abdominal pressure was maintained between 12-14 mmHg throughout the laparoscopic procedure.

Intraoperatively patients were monitored for NIBP, ECG, $EtCO_2$ and heart rate at every 5 min interval and any complications were treated. Hypotension defined as NIBP < 20% of the baseline or systolic BP < 90mmHg was treated by increasing the intravenous crystalloid infusion rate and additionally with vasoactive drugs. Bradycardia, defined as heart rate <20% of the baseline or less than 50 beats/min, was treated with 0.02mg/kg atropine.

After the release of pneumoperitoneum, infusion of the drug was stopped. 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 parameters were recorded and statistically analyzed. P value <0.05 was considered significant.

Patients were followed up for next 3 hrs in the post-anesthesia care unit (PACU) for any side effects of dexmedetomidine.

OBSERVATIONS AND RESULTS

Two groups were comparable with respect to age, gender, weight and duration of surgery (Table-I). There was no significant difference in preoperative values between the two groups (Table-II).

After 5 minutes of dexmedetomidine infusion, mean arterial pressure (MAP) decreased significantly in group I than in group II ($P<0.05$). MAP was significantly lower ($P<0.05$) during pneumoperitoneum, remained lower throughout the surgery and in postoperative period (Table-IV). Heart

rate also decreased significantly after 5 minutes of dexmedetomidine infusion and remained lower throughout pneumoperitoneum in group I (Table-III). Maximum fall in MAP and heart rate was at 30 minutes after dexmedetomidine infusion. No patient in group I had >20% fall in MAP. Only 2 patients in group I required atropine (Table V). There was no significant difference in SpO_2, $EtCO_2$ values in the two groups.

Table I: Patient characteristics and duration of surgery

	Group I	Group II	p value	Statistical Significance
Age(years)	36.4±11.1	35.9±10.8	>0.05	NS
Gender (M/F)	26/24	23/27		
Weight	58.9±9	58.4±9.8		
Duration of surgery	50.20± 3.91	48.80 ±11.94		

Table II: Pre-operative vitals in Group I and Group II

Parameter	Group I		Group II		p value	Statistical Significance
	Mean	SD	Mean	SD		
HR/min	84.96	10.16	85.60	7.67	0.72	NS
SBP(mmHg)	124.92	11.74	122.84	9.44	0.33	NS
DBP(mmHg)	79.64	5.93	77.56	5.47	0.07	NS
MBP(mmHg)	94.72	7.40	92.64	5.66	0.12	NS
SpO_2%	97.92	2.84	98.46	0.79	0.20	NS
$EtCO_2$	36.76	3.37	35.74	3.01	0.11	NS

Table III: Changes in HR at different time interval in Group I and Group II

Groups	Group I		Group II			Statistical significance
Time Interval	N	Mean ± SD	N	Mean ± SD	P value	
Preoperative	50	85.0±10.2	50	85.6±7.7	0.72	NS
Postintubation	50	113.06±9.72	50	109.6±9.48	0.07	NS
Postpneumoperitoneum						
M5	50	84.2±13.0	50	103.7±11.5	0.00	S
M10	50	84.2±13.1	50	100.3±14.1	0.00	S
M15	50	83.9±11.1	49	103.3±12.2	0.00	S
M20	50	83.3±10.5	48	99.8±10.1	0.00	S
M25	50	81.6±11.2	47	93.7±10.3	0.00	S
M30	50	80.2±11.5	47	97.5±10.6	0.00	S
M35	50	81.0±11.0	47	93.3±11.1	0.00	S
M40	50	81.4±10.9	47	97.7±10.6	0.00	S
M45	50	81.3±10.7	35	94.1±11.7	0.00	S
M50	50	82.5±10.8	25	94.6±11.1	0.00	S
M55	13	81.9±9.1	21	91.8±11.3	0.00	S
M60	5	83.2±10.4	11	94.4±9.2	0.00	S
M65	2	83.2±10.4	5	102.0±11.0	0.00	S
Postdeflation		84±10.3		103.12±11.71	0.00	S
Postextubation		82.04±11.45		100.86±10.97	0.00	S

Table IV: Changes in MBP at different time interval in Group I and Group II

Groups	Group I		Group II		P value	Statistical significance
Time Interval	N	Mean ± SD	N	Mean ± SD		
Preoperative	50	94.7±7.4	50	92.6±5.7	0.12	NS
Postintubation	50	101.026.85	50	98.446.62	0.06	NS
Postpneumoperitoneum						
M5	50	89.5±8.0	50	101.5±12.8	0.00	S
M10	50	87.3±8.5	50	102.0±14.9	0.00	S
M15	50	86.9±8.0	49	103.4±11.9	0.00	S
M20	50	86.0±8.6	48	100.2±9.5	0.00	S
M25	50	85.0±9.1	47	96.4±10.7	0.00	S
M30	50	84.2±9.1	47	99.5±12.6	0.00	S
M35	50	85.9±8.1	47	95.0±13.0	0.00	S
M40	50	85.7±7.2	47	98.7±11.5	0.00	S
M45	50	85.4±6.6	34	94.4±10.4	0.00	S
M50	50	88.3±7.3	25	94.4±8.1	0.00	S
M55	13	89.2±5.0	21	96.4±8.9	0.00	S
M60	5	88.0±4.6	11	94.8±7.1	0.00	S
M65	2	89.5±10.6	5	99.8±9.8	0.00	S
Postdeflation		92.66±7.72		103.46±11.13	0.00	S
Postextubation		87.66±8.68		100.64±10.77	0.00	S

Table V: Intraoperative use of Inj. Atropine in Group I and Group II

Drug	Group II (%)	Group I (%)	p value	Statistical significance
Atropine	0(0.0%)	2(4.0%)	0.15	NS

DISCUSSSION

Laparoscopic cholecystectomy is one of the routine procedures done in general surgery, with overall complication rate being less than 1.5%, and the mortality being less than 0.1%. However pneumoperitoneum and positioning required for this procedure alters the cardiovascular, respiratory, neuroendocrine and acid base physiology. Various surgical methods and anesthetic techniques have been used to avoid these complications but all have their own practical limitations.[11] Literatures are available regarding use of different drugs for hemodynamic stability in laparoscopic cholecystectomy but very few studies are available regarding use of dexmedetomidine.

Dexmedetomidine has gained popularity in patients on mechanical ventilator in intensive care settings because they need light sedation with fast awakening for their regular neurologic and cognitive assessment. Patients can be comfortably extubated while continuing dexmedetomidine infusion. α-2 adrenoceptor agonists are now being frequently used in anesthesia as they decrease sympathetic tone and attenuate the stress responses to intubation and surgery. Infusion doses of dexmedetomidine varying from 0.1 to 10 μg/kg/h[12,13] have been studied. The bolus or large doses of dexmedetomidine (1-2μg/kg) shows biphasic response that is transient increase followed by fall in blood pressure.[14] This could be due to stimulation of postsynaptic α-2 adrenoceptors on vascular smooth muscles and increase in systemic vascular resiatance. Even the low dose infusion of 0.25–0.5 μg/kg/h are effective in blunting stress response and decrease in systemic catecholamines.[14]

In our study dose of 0.2μg/kg/hr infusion had significant hemodynamic stability during intra and post-operative period. It is an effectve alternative to benzodiazepine and opioids in patients undergoing monitored anaesthesia care because of its analgesic, arousal sedation and lack of respiratory depression properties.[15] α 2 adrenoceptors are found in many sites in the central nervous system, highest densities in the locus ceruleus, the predominant noradrenergic nuclei of the brainstem which contributes to the maintenance of arousal or wakefullness. Presynaptic activation of the α 2 adrenoceptor in the locus ceruleus inhibits the release of norepinephrine and results in the sedative and hypnotic effects. Dexmedetomidine infusion also enables smooth extubation without causing hemodynamic instability, undue sedation and maintains plasma noradrenaline concentration.[16] Dexmedetomidine in a dose of 0.2μg/kg/hr is effective in blunting stress response to pneumoperitoneum.[17]

Bhattacharjee D. P. et al[4] showed the effects of Dexmedetomidine infusion (0.2 μg/kg/hour) for haemodynamic stability in patients undergoing laparoscopic cholecystectomy and found that heart rate in Dexmedetomidine group was significantly less after intubation and throughout the period of pneumoperitoneum. In our study the mean heart rate was also significantly lower in dexmedetomidine group. Only two patients in dexmedetomidine group required atropine for bradycardia.

Tufanogullari B. et al[13] compared three infusion doses of Dexmedetomidine 0.2, 0.4 and 0.8 µg/kg/hr with saline in morbidly obese patients undergoing laparoscopic bariatric surgery. MAP values after the start of the study drug infusion were significantly lower in the dexmedetomidine groups compared with the control group (P<0.05). They recommended dexmedetomidine infusion rate of 0.2µg/kg/hr to minimize the risk of adverse cardiovascular side effects.

In our study we found no significant change in SpO_2 values between both groups. None of the patient had SpO_2 less than 95%. Aho M. S. et al[18] concluded that dexmedetomidine doesn't effects oxygen saturation. In fact in his study, the patients who were treated with dexmedetomidine, showed higher oxygen saturation as compared to other groups. He postulated that by using dexmedetomidine, it is possible to reduce the amount of opiate narcotics needed for analgesia and to avoid some side effects of opioid treatment such as respiratory depression. Changes in $EtCO_2$ were almost comparable in both the groups (p>0.05) except at few time intervals. Two patients in dexmedetomidine group had rapid rise in $EtCO_2$ after pneumoperitoneum. Laparoscopic cholecystectomy was abandoned in both the cases and was converted to open cholecystectomy. In dexmedetomidine group values were comparable to the pre-operative values throughout the period of pneumoperitoneum, after deflation and extubation.

The patients in dexmedetomidine group required significantly lower concentrations of isoflurane. End tidal concentration required for maintenance of anaesthesia is 1.5 to 1.8%.[19] Isoflurane requirement decreases by 35-50% with dexmedetomidine.[20] It is also effective in reducing intraoperative requirement of opiods[21] and muscle relaxants, minimizing postoperative muscle weakness. Our findings were in accordance with study of Aho M. et al[18] and Talke P. et al[16] in which there was decrease in MAC and inhalational agent requirement with dexmedetomidine. Hall et al found 30% reduction in BIS score with infusion of dexmedetomidine at 0.2µg/kg/hour in healthy volunteers.[22] This massive reduction in anesthetic requirement is associated to central α-2 adrenergic receptors. Postoperative period was uneventful. None of the patients had respiratory depression or delayed extubation.

Centrally the activation of α 2 adrenoreceptors cause a reduction in peripheral sympathetic tone and an increase of vagaly induced reflex bradycardia and peripherally it causes stimulation of presynaptic α2 adrenoreceptors which leads to diminished release of norepinephrine from the nerve endings towards the vasculature thus reducing the peripheral sympathetic tone towards the heart. Dexmedetomidine therefore serves as an effective and specific regimen to blunt the cardiovascular response.

CONCLUSION

Low dose infusion of dexmedetomidine at the rate of 0.2 µg/kg/h without any bolus dose serves as a very useful anaesthesia adjuvant to control haemodynamic stress response to pneumoperitoneum and extubation in patients undergoing laparoscopic cholecystectomy.

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