Original Research Article

A comparison of dexmedetomidine and clonidine premedication in perioperative hemodynamic stability and postoperative analgesia in laparoscopic cholecystectomy

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ABSTRACT

Background: The aim of this study was to compare dexmedetomidine and clonidine premedication in perioperative hemodynamic stability and postoperative analgesia in laparoscopic cholecystectomy.

Materials and Methods: An observational study was conducted in Sir Sunderlal hospital, Banaras Hindu University. The study included ASA I-II patients undergoing laparoscopic cholecystectomy surgery. Patients undergoing general anaesthesia were included in the study. The control group received iv fentanyl, while patients in one experimental group received iv clonidine 1mcg/kg over 15 minutes, 30 minutes before and in another group received iv dexmedetomidine 1mcg/kg over 15 minutes, 30 minutes before the surgery. Heart Rate, SBP, MAP, DBP, ETCO₂, PCO₂ and Post-Operative Analgesia were compared for the 3 groups. Results were given as mean ± SD. Data collected were analysed using Student’s t-test. Differences were considered statistically significant if P values were <0.05.

Results: A total of 90 patients were included and 30 patients each were randomly assigned to one of the 3 groups. Patients who received dexmedetomidine had better haemodynamic control and post-operative analgesia. Patients who received clonidine had better haemodynamic control than control group but not better than the group who received dexmedetomidine.

Conclusion: We conclude that Alpha 2 agonists specially dexmedetomidine produce diverse responses including analgesia, anxiolysis, sedation and sympatholysis.

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1. Introduction

Laparoscopic surgery is a modern surgical technique involving insufflation of gas (usually CO₂) into the peritoneal cavity under pressure to separate organs from abdominal cavity. Laparoscopic cholecystectomy has revolutionised gall bladder surgeries and it has now become the gold standard for the treatment of cholelithiasis. Since the introduction of diagnostic laparoscopic procedures in early 1970s and the first laparoscopic cholecystectomy in the late 1980s laparoscopy has increased in both scope and volume. Increasing the success of laparoscopic surgery can be attributed to the fact that it results in multiple benefits compared with open procedures such as reduced trauma to the patient disturbance of homeostasis, morbidity, mortality, recovery time and hospital stay with consequent reduction in healthcare cost.

The anaesthesiologist’s traditional approach to anesthesia for laparoscopic cholecystectomy has been the emphasis on maintaining hemodynamic stability by avoiding hypertension, hypotension or tachycardia. The problem has been more complex than that has been originally thought and most of the hemodynamic instability is persistent during the duration of pneumoperitoneum...
Numerous agents and combination of agents has been used in an effort to minimize the hemodynamic instability during this period.

Laparoscopic surgeries require creation of pneumoperitoneum which is often produced by insufflations of carbon dioxide in the abdominal cavity by using automated flow controlled carbon dioxide insufflators which supply gas till the required intrabdominal pressure is reached, inflation pressure can be varied from 0-30 mm hg whereas the total gas flow volume can be set from 0-9.9L/min. Pain can prolong hospital stay and lead to increased morbidity which is particularly important now that many centres are performing this operation as a day case procedure. Pain may occur in the upper abdomen, lower abdomen, back or shoulders. It may be transient or persist for up to 3 days, shoulder pain may occur in as many as 63% or as few as 35% of patients.

Although the pain following a laparoscopic cholecystectomy is less intense than open surgery patients often suffer visceral pain with coughing respiratory movements and mobilization during the first hours and shoulder pain secondary to peritoneal insufflations after the eighth postoperative hour during the night after surgery. This can delay the patients autonomy lengthen the hospital stay and increase morbidity and costs. Multimodal analgesic techniques are therefore necessary to provide effective postoperative analgesia for several components of pain.

Many methods have been used to reduce postoperative pain including non-steroidal inflammatory drugs (NSAIDS), local anesthetics (LA) and opioids with varying success. Administration of intraperitoneal LA either during or after surgery is used by many surgeons as a method of reducing postoperative pain.

Alpha 2 agonists produce diverse responses including analgesia, anxiolysis, sedation and sympatholysis each of which has been reported in the treatment of surgical and chronic pain patients. Recently the food and drug administration of USA has registered a novel alpha 2 adrenergic agonist dexmedetomidine. Dexmedetomidine with an elimination half-life of two to three hours is a highly selective and potent and specific alpha 2 agonist (1620:1 alpha 2 to alpha 1) and is seven to ten times more selective for alpha 2 receptors compared to clonidine and has a shorter duration of action. Dexmedetomidine is considered full agonist at alpha 2 receptors as compared to clonidine dexmedetomidine also attenuates the hemodynamic response to tracheal intubation decreases plasma catecholamine concentration during anesthesia and decreases perioperative requirements of inhaled anesthetics. These characteristics make dexmedetomidine useful anesthetic adjunct during operation. Previous studies reported that intravenous use has a definitive role in postoperative analgesia through the reduction of opioid consumption.

As laparoscopic cholecystectomy is a routinely performed surgery it is desirable to have a stable intraoperative hemodynamic status. Hence in this study it has been attempted to compare the beneficial effect of alpha 2 agonist dexmedetomidine and clonidine in maintaining the perioperative hemodynamic parameters and reducing postoperative analgesic requirements in patients undergoing laparoscopic cholecystectomy.

2. Material and Methods

2.1. Study design

A prospective study was conducted from March 2015 to February 2016 at Institute of Medical Sciences, BHU Varanasi. The study was approved by the Ethical Committee and all patients or their relatives signed an informed consent.

2.2. Study population

This randomized prospective study was carried out on 90 adult patients scheduled for laparoscopic surgeries. Patients were included in the study based on the following criteria:

2.3. Inclusion criteria

1. Patients scheduled for elective laparoscopic surgery, with I-gel as airway device.
2. Patients aged between 30 and 70 years of either sex.

2.4. Exclusion criteria

1. Patients with upper respiratory tract infection, restrictive or obstructive lung disease.
2. Anticipated difficult airway with mouth opening less than 2 cm.
3. Hiatus hernia, Gastro-oesophageal reflux disease.
4. History of allergy to silicone and elastomer.
5. More than three attempts of unsuccessful I-Gel placement for securing airway.

Based on the above criteria 90 adult patients were included in the study. All were randomly allocated to the following groups of 30 each:

1. Group 1: patients were given i.v. fentanyl 2 mcg/kg during induction.
2. Group 2: patients were given i.v. clonidine 1 mcg/kg over 15 minutes 30 minutes before the induction.
3. Group 3: patients were given i.v. dexmedetomidine 1 mcg/kg over 15 minutes 30 minutes before the induction.
2.5. Study tool

It included pre-anæsthetic check-up, a clinical examination and Airway examination using LM-MAP Score (Look, MPG, Measurements 3-3-2-1, Atlanto-occipital extension, Pathological obstruction if any), investigations which included tests i.e. CBC (complete blood counts), FBS (fasting blood sugar), LFT (liver function test), RFT (renal function test), electrocardiogram (for patients over 40 years of age), chest X-ray. Pre-anæsthetic re-evaluation was done on the previous day of surgery.

2.6. Study technique

Informed written consent was taken from individual patients. All patients were pre-medicated with Tab. Alprazolam 0.25mg orally, Tab. Ranitidine 150mg orally and Tab. Metoclopramide 10mg orally on the night before surgery and 2hrs prior to surgery. A peripheral intravenous line with 18 gauze cannula was secured in one of the upper limb. Before arriving at the operation room all patients were preloaded with 500ml of Lactated Ringer solution. Patients received Inj. midazolam 30mcg/kg for all patients while group 2 received i.v. clonidine and group 3 received i.v. dexmedetomidine @ 1mcg/kg 30 minutes before induction respectively. In the operating room base line readings of Heart Rate (HR), Systolic Blood Pressure(SBP), Diastolic Blood Pressure(DBP), Mean Arterial Pressure(MAP), Oxygen Saturation(SaO2), and End Tidal CO2(ETCO2) was measured. Thereafter measurements of HR, SBP, DBP, MAP, ETCO2 were taken at intervals of 1, 5 and 10 minutes will be recorded. Patients were induced with 1% of Inj. Propofol 2mg/kg and depth of anaesthesia was monitored by loss of following verbal commands. Inj. Vecuronium 0.1mg/kg was administered. After bag and mask ventilation for three minutes, the appropriate sized airway device(I-Gel) was inserted. Effective ventilation with device was defined as a square wave capnograph trace and bilateral chest movements on manual ventilation. Patients were maintained with 33% of oxygen in air, isoflurane and intermittent dose of vecuronium. Perioperative analgesia was provided with Inj. Fentanyl 2 mcg/kg for group 1. The tidal volume and respiratory frequency was adjusted and intermittent positive pressure ventilation (IPPV) was continued by mechanical ventilator to maintain end tidal carbon dioxide level between 35-45 mm Hg. Pneumoperitoneum will be created by insufflation of carbon dioxide and operation table will be tilted 15degree reverse Trendelenburg position. Where the rate of gas (CO2) inflation was 6 litres/min to achieve an intraabdominal pressure of 10-14 mm of Hg. Pneumoperitoneum is maintained by a constant gas flow of 200 to 400ml/min. Any regurgitation of fluid through the gastric channel or airway tube was noted.

Heart rate (HR), non-invasive Systolic blood pressure (SBP), Diastolic Blood pressure (DBP), Mean arterial blood pressure (MAP), oxygen saturation (SpO2), end tidal carbon dioxide (EtCO2) will be recorded at 1,5 and 10 minutes after insertion of device. After pneumoperitoneum at 5,10,15,30,45,60,90 and 120 minutes and just after removal of device.

At the end of surgery residual neuromuscular block was reversed with appropriate dose of Inj. neostigmine and Inj. glycopyrrolate intravenously. After reversal patients were monitored in the post anaesthesia care area. And after 4 hours of completion of surgery again pain was assessed.

Complications such as incidence of any airway complications caused by supraglottic devices were managed accordingly.

2.7. Analysis of data

The statistical analysis was done using statistical software SPSS for windows (Version 23.0). Chi-square test was used for categorical variables. For comparing two groups of mean Student’s t test was used. P-value <0.05 is considered as statistically significant.

Patients of group 2 and 3 have better heart rate control before and after pneumoperitoneum than group 1, while among group 2 and 3 before pneumoperitoneum it is not significant but significant after pneumoperitoneum (p<0.005). (Table 1)

Systolic blood pressure after pneumoperitoneum is better controlled in group 2 and 3 than group 1(p<0.001) while when group 2 and 3 is compared group 3 results are significant(p=0.011), which means SBP is better controlled after pneumoperitoneum in group 3. (Table 4)

As the result shows Diastolic Blood Pressure before and after pneumoperitoneum is better controlled in group 2 and 3 in comparison of group 1(p<0.001) but it is insignificant when group 2 and 3 are compared. (Table 6)

As the result shows End Tidal CO2 and PCO2 before induction and before pneumoperitoneum is better controlled in group 2 and 3 in comparison of group 1(p<0.001) but it is insignificant when group 2 and 3 are compared. (Table 5)

3. Discussion

Pneumoperitoneum during laparoscopy produces significant hemodynamic changes which can be detrimental especially in elderly and hemodynamically compromised patients. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum.

This double blind randomised controlled prospective study was carried out in 90 patients to evaluate the effect of clonidine and dexmedetomidine premedication in attenuating hemodynamic stress response associated with pneumoperitoneum.

Clonidine an imidazole derivative is a selective alpha 2 adrenergic agonist. It is a potent antihypertensive drug.
Table 1:

|                      | Group 1 Mean±SD | Group 2 Mean±SD | Group 3 Mean±SD | f-value | p-value |
|----------------------|-----------------|-----------------|-----------------|---------|---------|
| HR_bef_ind           | 83.97±9.590     | 79.40±5.805     | 80.30±8.883     | 2.574   | 0.082   |
| HR_bef_penu          | 79.40±9.485     | 66.47±4.554     | 70.73±8.614     | 21.138  | 0.000   |
| HR_aft_pneu          | 93.17±5.947     | 68.26±4.293     | 73.54±9.135     | 106.231 | 0.000   |

Group comparison

Table 2:

|                      | Group 1 Mean±SD | Group 2 Mean±SD | t-value | p-value |
|----------------------|-----------------|-----------------|---------|---------|
| HR_aft_ind           | 66.47±4.554     | 71.17±8.363     | -2.703  | 0.009   |
| SBP_aft_ind          | 105.07±5.369    | 112.90±8.376    | -4.312  | 0.000   |
| DBP_aft_ind          | 65.53±4.840     | 88.50±110.064   | -1.142  | 0.258   |
| EtCO2_aft_ind        | 27.87±2.921     | 28.00±3.248     | -0.167  | 0.868   |
| PCO2_aft_ind         | 29.13±2.837     | 29.73±3.205     | -0.768  | 0.446   |

Table 3:

|                      | Group 1 Mean±SD | Group 2 Mean±SD | Group 3 Mean±SD | f-value | p-value |
|----------------------|-----------------|-----------------|-----------------|---------|---------|
| SBP_bef_ind          | 121.33±10.984   | 123.67±10.307   | 124.37±9.031    | 0.736   | 0.482   |
| SBP_bef_penu         | 116.80±7.959    | 112.60±7.740    | 113.07±8.788    | 2.379   | 0.099   |
| SBP_aft_pneu         | 145.03±11.105   | 115.11±7.470    | 122.90±10.324   | 71.016  | 0.000   |

Group comparison

Table 4:

|                      | Group 1 Mean±SD | Group 2 Mean±SD | Group 3 Mean±SD | f-value | p-value |
|----------------------|-----------------|-----------------|-----------------|---------|---------|
| DBP_bef_ind          | 80.90±8.130     | 80.07±7.656     | 76.60±7.518     | 2.582   | 0.081   |
| DBP_aft_pneu         | 91.90±5.095     | 72.37±6.319     | 75.03±6.139     | 95.535  | 0.000   |
| DBP_bef_penu         | 77.00±6.363     | 70.13±6.078     | 68.50±7.314     | 13.985  | 0.000   |

Group comparison

Table 5:

|                      | Group 1 Mean±SD | Group 2 Mean±SD | Group 3 Mean±SD | f-value | p-value |
|----------------------|-----------------|-----------------|-----------------|---------|---------|
| EtCO2_bef_ind        | 31.87±3.776     | 27.03±3.419     | 28.23±3.181     | 15.807  | 0.000   |
| EtCO2_bef_penu       | 34.30±4.308     | 28.63±2.580     | 27.97±3.253     | 30.446  | 0.000   |
| EtCO2_aft_pneu       | 40.60±10.611    | 38.43±2.542     | 39.57±10.210    | 0.473   | 0.625   |
Table 6:

|                      | Group 1 Mean±SD | Group 2 Mean±SD | Group 3 Mean±SD | f-value | p-value |
|----------------------|-----------------|-----------------|-----------------|---------|---------|
| PCO2_bef_ind         | 35.63±3.819     | 27.90±2.881     | 30.23±3.093     | 43.641  | 0.000   |
| PCO2_bef_penu        | 37.73±4.152     | 30.37±3.157     | 30.00±3.248     | 45.377  | 0.000   |
| PCO2_aft_pneu        | 43.70±10.192    | 40.57±2.788     | 41.63±10.002    | 1.079   | 0.344   |

Group comparison

3.1. Baseline comparison

Baseline comparison between the 3 study groups revealed that the groups were comparable with respect to age, sex, weight, total surgery time, and total anesthesia time. There was no statistically significant variation in these baseline characteristics among the three groups.

3.2. Clonidine vs control

Statistically significant differences were observed in the HR, MAP, and requirement of isoflurane between control and clonidine group. The HR and MAP were found to be lower in clonidine group and the patients in group 2 required lesser isoflurane.

3.3. Dexmedetomidine versus control

Statistically significant differences were observed in the HR, MAP, and requirement of isoflurane between control and dexmedetomidine group. The HR and MAP were found to be lower in dexmedetomidine group.

3.4. Clonidine versus dexmedetomidine

Although decrease in HR appeared more in dexmedetomidine after induction and creation of pneumoperitoneum no statistically significant difference was found in MAP requirement of isoflurane and requirement of atropine between the two groups.

The alpha 2 agonists including clonidine and dexmedetomidine decrease central sympathetic outflow by acting like a brake and modify intraoperative cardiovascular and endocrine responses favourably to surgical stimuli of laryngoscopy and laparoscopy. Both clonidine and dexmedetomidine have been shown to reduce sympathetic nervous system activity and plasma catecholamine concentrations.

Clonidine with an elimination half-life of 6 to 10 hours is a centrally acting selective partial alpha 2 agonist. It is known to induce sedation decrease anesthetic drug requirement and improve perioperative hemodynamics by attenuating blood pressure and heart rate responses to surgical stimulation and protecting against perioperative myocardial ischemia. It provides sympathoadrenal stability and suppresses rennin angiotensin activity Chiruvella et al. studied IV 1 mcg/kg of dexmedetomidine and clonidine for attenuation of stress responses during laparoscopic cholecystectomy and found dexmedetomidine more effective than clonidine however chances of hypotension and bradycardia were more with dexmedetomidine. Our study showed similar results.

Kumar et al. compared the effects of dexmedetomidine and clonidine premedication in 60 patients undergoing laparoscopic cholecystectomy and found that both the drugs were effective in attenuating the hemodynamic response to pneumoperitoneum with equal efficacy. But in our study dexmedetomidine was more effective even though the dose of drugs given were same.

Tripathi et al. found that Clonidine, 2 µg/kg intravenously, 30 min before induction is safe and effective in preventing the hemodynamic stress response during laparoscopic cholecystectomy.
Aho et al.\textsuperscript{12} used 3 $\mu$g.kg\(^{-1}\) and 4.5 $\mu$g.kg\(^{-1}\) clonidine for suppression of haemodynamic response to pneumoperitoneum. Rise in blood pressure and heart rate was less in both the groups but 4.5 $\mu$g.kg\(^{-1}\) clonidine produced greater fall in mean arterial pressure before induction. But in our study the fall in MAP was less as the dose of both the drugs used was less.

Joris et al.\textsuperscript{13} sed very high dose of clonidine (8 $\mu$g.kg\(^{-1}\)) for reducing the level of catecholamine and vasopressin following pneumoperitoneum. Malek et al.\textsuperscript{14} used 150 $\mu$g of clonidine as i.v. infusion and intramuscularly while Sung et al. and Yu et al. used 150 $\mu$g of oral clonidine as premedication for maintenance of haemodynamic stability during pneumoperitoneum.

In our study we found that heart rate and mean arterial pressure were significantly lower in dexmedetomidine group when compared to saline group than the clonidine group. We used a lower dose of dexmedetomidine and clonidine anticipating untoward effects. However a dose-response curve is required to ascertain the role of above two drugs, which could not be done in the present study.

Joris JS et al.\textsuperscript{13} found that pneumoperitoneum results in an increase in MAP, SVR and PVR and a decrease in cardiac output. The increase in SVR is associated with a marked release of vasopressin and catecholamines. Clonidine given before pneumoperitoneum reduces the release of catecholamine and provides intraoperative hemodynamic stability clonidine before creation of pneumoperitoneum reduces catecholamine release thus significantly attenuated the increase in mean arterial pressure and heart rate in comparison to saline in a study where patients received 8 mcg/kg clonidine infused over 1 hour before pneumoperitoneum. We have used clonidine 1mcg/kg and our findings have correlated with this study.

The possible limitations of the study were the low dose of drugs used, small sample size, inability to monitor the serum concentration of the drugs. On the contrary strength of the study is in the lack of previous reports as prospective randomised trials in comparing the effects of above two drugs.

4. Conclusion
The result of present study showed that 1mcg/kg of dexmedetomidine showed better control of hemodynamics as compared to 1mcg/kg of clonidine.

5. Source of Funding
None.

6. Conflict of Interest
The author(s) declare(s) that there is no conflict of interest regarding the publication of this article.

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