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Evaluation of Efficacy of Two Different Doses of Dexmedetomidine Infusion on the Peri-operative Hemodynamic Response and Dose Sparing Effect on the Anesthetics in Patient's Undergoing Laparoscopic Cholecystectomy under General Anesthesia

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Abstract

Introduction: Intravenous use of dexmedetomidine in the peri-operative period had been found to decrease serum catecholamine levels by 90%, to blunt the hemodynamic response to laryngoscopy, tracheal intubation, pneumoperitoneum and extubation, to provide sedation without respiratory depression and to decrease post-operative analgesic requirements. *Aims:* We aimed primarily to evaluate the effects of two different doses dexmedetomidine infusion on hemodynamic response to critical incidences such as laryngoscopy, endotracheal intubation, creation of pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. The secondary aims were to study the dose sparing effect of dexmedetomidine on anesthetic drugs used. *Methods:* Hundred patients of American Society of Anesthesiologists (ASA) physical Grades I and II undergoing laparoscopic cholecystectomy were randomly allocated into two Groups of 50 patients each. Group A patients received dexmedetomidine infusion at 1 *µg/kg* and Group B patients received dexmedetomidine infusion at 0.6 *µ/kg* both over twenty minutes, starting 20 *min* before induction and thereafter, dexmedetomedine infusion continued at 0.2 *µ/kg/hr* in both the Groups till end of surgery. Parameters noted were pulse rate, mean arterial pressure, oxygen saturation, post-operative sedation and anesthetic drugs requirements. Chi-square test was used for qualitative data were applied. *Results:* Dexmedetomidine 1 *µg/kg* is more effective compared to Dexmedetomidine at 0.6 *µ/kg* in attenuating the tachycardia response to laryngoscopy, intubation and pneumoperitonem. Also, Dexmedetomidine at 1 *µg/kg* has a better dose sparing effect on anesthetic drugs used intra-operatively than Dexmedetomidine at 0.6 *µg/kg*. Both the Dexmedetomidine Groups provide light and arousable sedation post-operatively without respiratory depression. *Conclusion:* Dexmedetomidine infusion in the dose of 1 *µg/kg* effectively attenuates hemodynamic stress response during laparoscopic surgery with reduction in post-operative analgesic requirements.

Keywords: Laparoscopy; Cholecystectomy; Pneumoperitoneum; Dexmedetomidine.

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Introduction

Laproscopic surgery is one of most important diagnostic and therapeutic tools in the present surgical era. Since 1987, when the first laproscopic cholecystectomy was successfully performed by Philipe Mouret, this has become gold standard.[1]

The benefits of minimal access techniques include

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less pain, early mobilization, shorter hospital stay and better cosmetic results, which have further increased its applications. During general anesthesia laryngoscopy, tracheal intubation and extubation are the critical events provoking transient, but marked sympathoadernal response manifesting as hypertension and tachycardia.[2] In addition, in laparoscopic surgery CO_2 is routinely used to create pneumoperitoneum, which causes increased plasma level of catecholamine and vasopressin. Elevation of intra-abdominal pressure with raised diaphragm causes various adverse effects on cardiovascular system such as decreased cardiac output, elevated arterial pressure and increased systemic and pulmonary vascular resistance leading to hypertension and tachycardia. Hence, a drug, which can blunt hemodynamic response to laryngoscopy, intubation and pneumoperitoneum without having any adverse effects like respiratory depression and post-operative nausea and vomiting, was required for purpose.[3]

Alpha-2 adrenergic agonists have both analgesic and sedative properties. Dexmedetomidine is a highly selective alpha-2 adrenergic agonist with an affinity of eight times greater than Clonidine. Intravenous use of dexmedetomidine in the peri-operative period had been found to decrease serum catecholamine levels by 90%[4] to blunt the hemodynamic response to laryngoscopy, tracheal intubation, pneumoperitoneum and extubation,[5] to provide sedation without respiratory depression[3] and to decrease post-operative analgesic requirements.[6]

The anesthetic, analgesic drugs and muscle relaxant dose requirement get reduced to huge extent by the use of Dexmedetomidine, which is shown by many studies.[3]

Many studies have been conducted with dose of dexmedetomidine at *1 μg/kg*, *0.6 μg/kg* and *0.2 μg/kg*.[7,8] But not many studies have been conducted to compare the efficacy between *1 μg/kg* and *0.6 μg/kg*.

Hence, a study was undertaken to compare the efficacy between *0.6 μ/kg* and *1 μg/kg* of dexmedetomidine in laparoscopic surgeries to evaluate hemodynamic variables, anesthetic and analgesic drug requirement and sedation post-operatively.

Aims

We aimed primarily to evaluate the effects of two different doses dexmedetomidine infusion on hemodynamic response to critical incidences such as laryngoscopy, endotracheal intubation, creation of pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. The secondary aims were to study the dose sparing effect of dexmedetomidine on anesthetic drugs used.

Materials and Methods

Following approval of institutional ethical committee, 100 patients between *18* and *65 years*, of either sex belonging to ASA 1 and 2 posted for laparoscopic cholecystectomy. It was a prospective, randomised, double blind, placebo controlled clinical study. Patients with decreased autonomic control such as the elderly, diabetic patients, patients with chronic hypertension or severe cardiac disease, patients on drugs like β blockers or calcium channel blockers, pregnant or lactating women, patients with history of allergy to egg proteins and drugs particularly α^2 agonists were not considered for the study. Patients will be randomly allocated into two Groups of 50 each, using sealed envelope technique:

Group A: Receives *1 μ/kg* of dexmedetomedine infusion over *twenty minutes*;

Group B: Receives *0.6 μ/kg* of dexmedetomedine infusion over *twenty minutes.*

All patients on arrival to the operation theatre, two intravenous lines will be secured with a 18 G or 20 G cannulas one for intravenous fluid and another for administering the test drug. Injection Dexmedetomidine prepared in infusion syringes, loading dose of *0.6 μ/kg* for one Group, *1 μ/kg* for another Group. To prepare infusion, dexmedetomidine *0.5 ml* containing *50 μg* of the drug was withdrawn in a *20 ml* syringe and diluted to *20 ml*. depending on the weight of the patient, the pump was set so as to deliver the targeted infusion rate. After the setting the infusion pump, it was covered with black cloth so that, the assessor did not come to know about the grouping of the patient. Thus, the syringe was same, volume of prepared solution was same, only the rate of injection was different according to the weight and group of patient. Thus, the assessor and the patient were unaware of the group. *500 ml* ringer lactate infusion started in one IV line and infused over *20 minutes* prior to induction for both the groups with respective doses.

Pulse oximeter, non-invasive blood pressure and ECG monitors, BIS will be connected. Base line heart rate, blood pressure, SpO_2, Respiratory rate and BIS values will be recorded before pre-medication. Sedation level will be assessed by Modified Ramsay

Sedation scale. *Twenty minutes* after starting the drug infusion, pre-oxygenation was performed for *3 min*. Both groups were Pre-medicated with Inj glycopyrrolate *0.2 mg*, Inj midazolam *0.5 mg*, Inj fentanyl *1 μ/kg* (IV). Anesthesia was induced with Inj propofol as a 1% solution till loss of eye lash reflex occurred and dose of propofol required for loss of eye lash reflex recorded and Inj vecuronium *0.1 mg/kg*. Tracheal intubation was achieved with appropriate sized cuffed endotracheal tube. Thereafter, dexmedetomedine infusion started at *0.2 μ/kg/hr* in both the groups.

Patient will be maintained with O_2:N_2O mixture of 50:50 connected to closed circuit and inhalational agent isoflurane varying between 0.2%–1% to maintain depth of anesthesia. Monitoring BIS values between 40–60. Muscle relaxation will be maintained with Inj vecuronium. Total dose of vecuronium required for the surgery recorded. Test drug infusion will be discontinued on deflation of pneumoperitoneum.

Patient will be reversed with Inj neostigmine *0.05 mg/kg* and Inj glycopyrrolate *8 mcg/kg* (IV) and will be extubated after adequate return of muscle power and fulfilling major extubation criteria.

Intra-operative monitoring will be documented during pre-induction, after the loading dose of dexmedetomedine, at the induction of anesthesia. *1* and *3 min* after laryngoscopy and intubation, and at pneumoperitoneum and every *15 min* till the end of surgery and continued during extubation and post-operatively for *2 hrs*. Any side effects like Hypotension (MAP < 30% of baseline, treated with bolus intravenous ringer lactate solution and Inj ephedrine *6 mg* IV), Bradycardia (heart rate < 60 with Inj atropine *0.01 mg/kg -0.02 mg/kg* IV), Respiratory depression, post-operative nausea and vomiting will noted and treated patients will be observed in the recovery room for *2 hrs* before shifting to ward. Observer and the patient.

To detect a minimum of 20% difference in dexmedetomedine *0.6 μ/kg* and dexmedetomidine *1 μ/kg* minimum of 48 patients will be required when alpha error is kept at 0.05 and power of study at 80%. So, sample size was estimated as 50 patients in each group. Chi-square test was used for qualitative data (sex, ASA grade), PR, blood pressure, oxygen saturation, end tidal carbon dioxide etc., were compared within the group against baseline values using paired *t*-test. The results were expressed as mean ± standard deviation. $p > 0.05$ was considered insignificant, < 0.05 as significant and highly significant if < 0.001.

Results

Demographic data (age, sex, weight and ASA grading) of the patients were comparable in both the study groups ($p > 0.05$). Base line of hemodynamic data (HR, SBP, DBP and MAP) were comparable in both the groups and statistically insignificant ($p > 0.05$).

The baseline mean heart rate (Group A = *84 bpm*, Group B = *89 bpm*) in both the groups were comparable prior to starting the study drugs. There was a significant fall in heart rate in Group A compared to Group B after the starting dexmedetomidine infusion upto *10 minutes*, *1 min* after induction, *1 min* after laryngoscopy and intubation and *1 min* after initiation of pneumoperitoneum ($p < 0.05$), (Tables 1–7).

Baseline systolic blood pressure (mm hg) in Group A (mean = 127.2) and Group B (mean = 125.9) were comparable. Baseline diastolic blood pressure (*mm Hg*) in Group A (mean = 79.5) and Group B (mean = 79) were also comparable ($p > 0.05$).

The Mean Arterial Pressure (MAP) decreased significantly in Group A compared Group B. No further significant changes were observed immediately after induction. After intubation and initiation of pneumoperitoneum, the heart rate and MAP decreased significantly below the pre-infusion level in both the groups, though, this decrease was more in Group A than B but it was not statistically significant. ($p > 0.05$). None of the patients in both the groups developed severe bradycardia, hypotension or hypertension requiring treatment.

In group, A mean dose of Propofol required for loss of eye lash reflex is *84 ± 3.62 mg* (*1.52 mg/kg*) and in Group B mean dose is *95 ± 4.22 mg* (*1.72 mg/kg*). Statistical evaluation between the groups showed that the statistically significant reduction in dose of Propofol required for induction in Group A, ($p < 0.05$).

In group, A dose of vecuronium bromide required for muscle relaxation is *5.64 ± 1.52 mg* (duration of surgery: *99 minutes*) and in Group B dose of vecuronium bromide required for muscle relaxation is *8.48 ± 1.91 mg* (duration of surgery:100.5 *minutes*). Statistical evaluation between the groups showed that the statistically significant reduction in dose of vecuronium bromide required for muscle relaxation in Group A ($p < 0.05$).

The mean sedation scores were more in Group A than Group B. None of the patients in both the dexmedetomidine groups developed siginificant sedation levels and the patients were co-operative, oriented and tranquil all the time.

Tachycardia and hypertension were seen in 3 patients of Group A compared to 2 patients of group Group B. Hypotension was noted in 1 patient of Group A and reflex bradycardia was seen in 1 patient of Group A.

Table 1: Demographic characteristics and duration of surgery and anesthesia (mean ± SD)

Parameters	Group A	Group B	p
Age (yrs)	38.3 ± 11.676	38.02 ± 10.693	NS
Sex			
Male	24	27	NS
Female	26	23	NS
Mean body weight in *Kg* ± SD	56.12 ± 6.15	55.34 ± 7.56	NS
Duration of Surgery	99 ± 3.85	100.5 ± 4.12	NS

Table 2: Changes in HR (beats *per minute*) (mean ± SD)

Time	Group A	Group B	p
Before starting infusion	84.3 ± 16.5	89 ± 11.9	NS
10 min after starting infusion	67.3 ± 9.4	75.2 ± 11.1	< 0.05
1 min after induction	66.5 ± 6.6	70.2 ± 4.1	NS
1 min after laryngoscopy and intubation	73.4 ± 8.8	84 ± 7.8	< 0.05
After Pneumoperitoneum			
1 min	74.1 ± 4	84.5 ± 4.5	< 0.05
15 min	72.5 ± 10.1	78.6 ± 8.4	NS
30 min	72.4 ± 13	76.3 ± 16.8	NS
45 min	71.2 ± 5.4	75.1 ± 2.1	NS
60 min	73.6 ± 6.6	77.2 ± 3.2	NS

Table 3: Changes in MAP (*mm* of *Hg*) (mean ± SD)

Time	Group A	Group B	p
Before starting infusion	97.12 ± 9.21	98.5 ± 11.32	NS
10 min after starting infusion	96.54 ± 4.2	98.2 ± 10.22	NS
1 min after induction	96.45 ± 5.307	97.53 ± 8.2	NS
1 min after laryngoscopy and intubation	102.21 ± 9.79	103.34 ± 4.5	NS
After Pneumoperitoneum			
1 min	100.2 ± 7.34	101.3 ± 5.4	NS
15 min	99.2 ± 3.3	100.2 ± 6.2	NS
30 min	98.63 ± 4.3	98.72 ± 9.9	NS
45 min	98.88 ± 5.5	98.92 ± 1.1	NS
60 min	97.56 ± 6.8	98.12 ± 2.34	NS

Table 4: Dose of Propofol required for induction

Groups	Mean Dose of Propofol required for induction (*mg*)
Group A	*84 ± 3.62 mg* (*1.52 mg/kg*)
Group B	*95 ± 4.22 mg* (*1.72 mg/kg*)
p value	< 0.05

Table 5: Dose of Vecuronium bromide required for muscle relaxation

Groups	Dose of Vecuronium bromide required for muscle Relaxation (*mg*)
Group A	*5.64 ± 1.52 mg*
Group B	*8.48 ± 1.91 mg*
p value	< 0.05

Table 6: Showing the sedation score

Groups	Sedation score
Group A	2.74 ± 0.5
Group B	2.52 ± 0.4
p value	> 0.05

Table 7: Post-operative analgesic requirements

Groups	Time for first rescue analgesic requirement (*in min*)
Group A	255
Group B	187

Discussion

In laparoscopic surgery pneumoperitoneum created using Carbon-di-oxide. Various hemodynamic changes can obscure the operative area and make the surgery difficult, which may lead to complications, resulting in increased morbidity and prolonged post-operative hospital stay. Various physiological methods and pharmacological agents have been used for controlling hemodynamics in laparoscopic surgery with varying success. Dexmedetomidine, a α^2 agonist, provides dose dependent sedation, analgesia, sympatholysis, anxiolysis and controlled hypotension without relevant respiratory depression. Dexmedetomidine has also been found to be effective in attenuating pressor response to intubation and pneumoperitoneum.

Activation of α^2 A receptors in brain stem vasomotor centre results in suppression of norepinephrine release, hypotension and bradycardia. Stimulation of α^2 A and α^2 C in locus ceruleus causes sedation. In the spinal cord, activation of both α^2 A and α^2 C receptors directly reduce pain transmission by reducing release of substance *p*.

Dexmedetomidine infusion rates varying from *0.1* to *10 mcg/kg/hr* have been studied. With higher dose infusion of dexmedetomidine, high incidence of adverse cardiac effects have been observed. Higher doses of Dexmedetomidine can cause hypotension and bradycardia. Pre-loading with intravenous fluid prior to administration of dexmedetomidine reduces the incidence of hypotension. A biphasic

response on blood pressure occurs with a bolus dose.[4] Initially, there occurs hypertension followed by fall in blood pressure. This response is seen often more in young and healthy patients.[9] Stimulation of α^2 B receptors in vascular smooth muscles is said to be responsible for this.

Many studies have been conducted with dose of dexmedetomidine at *1 µ/kg*, *0.6 µ/kg* and *0.2 µ/kg*. But not many studies have been done to compare efficacy between *1 mcg/kg* and *0.6 µ/kg*. Hence, a study was undertaken to compare the efficacy between *0.6 µ/kg* and *1 µ/kg* of dexmedetomidine in laparoscopic surgeries to evaluate hemodynamic variables, anesthetic and analgesic drug requirement and sedation post-operatively. In our study, both the groups were comparable with regards to mean age, weight and sex.

In our study, we noted hemodynamic response during critical incidences like laryngoscopy and intubation, pneumoperitoneum. From our study, we observed Dexmedetomidine attenuates this sympathoadrenal response and provides hemodynamic stability. However, Dexmedetomidine at a dose of *1 µg/kg* appears to be more effective in attenuating tachycardia response compared to *0.6 µg/kg*. Statistically significant differences were noted between the groups, *1 min* following laryngoscopy and intubation and pneumoperitoneum. At other intervals values were comparable.

Dexmedetomidine at doses of *1* and *0.6 µg/kg* used in our study, were effective in attenuating the blood pressure to laryngoscopy and intubation and pneumoperitoneum. Statistically no significant differences were noted between the groups Dexmedetomidine potentiates anesthetic effects of all intra-operative anesthetics, regardless of the method of administration. The profound reduction in anesthetic requirement was shown to be mediated through central α^2 adrenergic receptors. Dose sparing effects with Dexmedetomidine also noted with opioids and inhalational agents.[10–12]

We studied the total dose of propofol required for induction in each group. In Dexmedetomidine *1 µg/kg* group dose of propofol required for induction was *84 ± 3.62 mg* (*1.52 mg/kg*) and in Dexmedetomidine *0.6 µg/kg* group dose required was *95 ± 4.22 mg* (*1.72 mg/kg*). This is statistically and clinically significant ($p < 0.05$).

We also studied the total dose of vecuronium required in each group. We found in Dexmedetomidine *0.6 µ/kg* group dose of vecuronium bromide required for muscle relaxation was *8.48 mg* (duration of surgery: *99 minutes*) and in Dexmedetomidine *1 µ/kg* group dose required was *5.64 mg* (duration of surgery: *100.5 minutes min*). There is a significant reduction in the dose of vecuronium required in the Dexmedetomidine *1 µg/kg* (< 0.05) compared to the control group. Since, duration of action of vecuronium depends on the dose given, we can expect a prolongation of action of vecuronium by Dexmedetomidine if similar doses were used in both the groups. Limittation here is nerve stimulators were not used due to unavailability in our hospital.

Dexmedetomidine is known to produce arousable sedation by its action on locus coeruleus nucleus without producing any respiratory depression. No patient in our study in both the dexmedetomidine groups had any post operative respiratory depression. Sedation scores were slightly higher in Dexmedetomidine *1 µg/kg* group compared to *0.6 µg/kg* group and it was not statistically significant.

We also observed an increase in the time to receive first rescue analgesia and a decrease in total analgesic requirements in first *24h* post-operatively in both dexmedetomidine Groups.

Conclusion

Dexmedetomidine *1 µg/kg* is more effective compared to Dexmedetomidine at *0.6 µ/kg* in attenuating the tachycardia response to laryngoscopy, intubation and pneumoperitonem. Also, Dexmedetomidine at *1 µg/kg* has a better dose sparing effect on anesthetic drugs used intra-operatively than Dexmedetomidine at *0.6 µg/kg*. Both the Dexmedetomidine Groups provide light and arousable sedation post-operatively without respiratory depression.

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