ORIGINAL RESEARCH

A Comparative Evaluation Of Intravenous Clonidine And Dexmedetomidine On Perioperative Hemodynamic During Pneumoperitoneum In Laparoscopic Cholecystectomy

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ABSTRACT
Background: Multiple agents are used for laparoscopic cholecystectomy since laparoscopic cholecystectomy is routinely performed surgery and desirable to have a stable intraoperative hemodynamic status by avoiding hypotension, hypertension or tachycardia. The search for ideal agent is still ongoing, alpha -2 adrenergic agonist have created interest in manner. So, the present study was conducted to compare the beneficial effect of clonidine and dexmedetomidine during laparoscopic cholecystectomy in maintain perioperative cardiovascular stability.
Methods: The present double blind randomized, prospective clinical study was carried out among patients scheduled for elective laparoscopic cholecystectomy under general anaesthesia for a duration of 2 years. The sample size was calculated as 90 using formula: $n=4pq/d^2$ and were divided equally into groups A (control), group B (clonidine) and group C (dexmedetomidine). Preanesthetic assessment of all the selected patients were done with complete history, general examination, airway assessment, systemic examination along with laboratory investigations. During perioperative period, hemodynamic parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded various intervals.
Results: Increase in heart rate was statistically insignificant in all the groups at baseline (B) and just after induction (D0).After infusion of drugs, increase in heart rate was significantly lower in all the intervals in Dexmedetomidine group and Clonidine group comparing with Control group.On comparing dexmedetomidine group with clonidine group, insignificant fall (p>0.05) in DBP were observed at all intervals except at 30 minutes after pneumoperitoneum (APN30) and after reversal(DBP_AR).While comparing Dexmedetomidine group with clonidine group, insignificant fall (p>0.05) in SBP and MAP were observed at all intervals except at 50 minutes after

pneumoperitoneum (APN50).While comparing Clonidine with Dexmedetomidine, significantly decrease heart rate was observed in dexmedetomidine group.
Conclusion: Creation of pneumoperitoneum in laparoscopic abdominal surgeries produces significant increase of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP). During pneumoperitoneum in laparoscopic abdominal surgeries both intravenous clonidine and intravenous dexmedetomidine results to attenuate in all hemodynamic parameters (HR, SBP, DBP and MAP) During pneumoperitoneum in laparoscopic surgeries heart rate is better controlled by dexmedetomidine.
Keywords: Efficacy, pneumoperitoneum, cholecystectomy, hemodynamic, clonidine

INTRODUCTION

Laparoscopic cholecystectomy surgery is one of the most commonly undertaken procedure in general surgery with the overall complication rate being less than 1.5% and the mortality being less than 0.1% [1,2].The anaesthetist's approach to anaesthesia for laparoscopic cholecystectomy surgeries has been giving attention on maintaining hemodynamic stability by avoiding hypotension, hypertension or tachycardia. The duration of pneumoperitoneum (PNP), likely carbon dioxide (CO_2) insufflations, and patient positioning are also associated with hemodynamic instabilitycharacterized by decreased cardiac output, increased arterial pressures, increased systemic vascular resistance (SVR) and pulmonary vascular resistance(PVR) [3,4].
Various anaesthetic interventions like use combination of epidural and general anaesthesiaor epidural or segmental spinalcontrolled increase of intrathoracic blood volume (ITBV) by intravenous fluidsand pharmacological ways have been used by anaesthetist over the years to prevent or attenuate these unfavourable hemodynamic changes associated with pneumoperitoneum [5,6,7].
Clonidine a centrally acting selective partial α- 2 agonist is induce sedation, that hampers the release of catecholamine and vasopressin, thereby regulate the hemodynamic changes induced by pneumoperitoneum, increases cardiac baroreceptor reflex sensitivity to increase in systolic blood pressure and stabilizes blood pressure in patients undergoing laparoscopic cholecystectomy [8,9].Also, dexmedetomidine is another highly selective and potent specific α-2 agonist. It is seven to ten times more selective for α-2 receptors compared to clonidine and has lesser duration of action. Dexmedetomidine maintains blood pressure and heart rate and reduces the opioid requirements during pneumoperitoneum in laparoscopicsurgeries [10,11].
So, the present study was conducted withan aim to evaluate the efficacy of intravenous clonidine and dexmedetomidine in maintaining the perioperative hemodynamic parameters [systolic blood pressure (SBP),diastolic blood pressure (DBP),mean arterial pressure (MAP), heart rate (HR)] during pneumoperitoneum in laparoscopic cholecystectomy.

MATERIALS AND METHODS
STUDY DESIGN AND STUDY SUBJECTS

After approval from the institutional ethical committee, the present double blind randomized, prospective clinical study was carried out among patients (age: 20-50 years and ASA grade I and II) scheduled for elective laparoscopic cholecystectomy under general anaesthesia of in Saraswathi Institute of Medical Sciences, Anwarpur, Hapur (Uttar Pradesh) for a duration of 2 years (December 2020 to November 2022).

SAMPLE SIZE

The sample size was calculated as 90 using formula:$n=4pq/d^2$, where, n is sample size, p = 66% (prevalence of hemodynamic instability among patients during elective laparoscopic cholecystectomy), q=100-p and d is standard error = 10%. Patients with BMI>30, undergoing laparoscopic to open surgery conversion intraoperatively, allergy to the study drugs, cardiopulmonary and respiratory disorders, onantihypertensive drugs, with psychiatric illness, with renal and hepatic dysfunction, pregnant and lactating females were excluded from the study.

ANAESTHETIC METHODS

A written informed consent was taken from patients who meet the inclusion criteria prior to intervention and a standardized protocol for anaesthesiawasfollowed for all cases.So, a total of 90 patients were enrolled in the study and were divided into 3 groups i.e. 30 patients in each group using computer generated randomization tables[Group A: 50 ml normal saline over a period of 10 minutes after induction and before pneumoperitoneum (PNP), followed by a continuous slow infusion at the rate of 0.5 ml/kg/hr; Group B: Clonidine 2μg/kg in 50ml normal saline over a period of 10 minutes after induction and before PNP, followed by a continuous infusion at the rate of 0.5 ml/kg/hr. (2 μg/kg/hr); and Group C: Dexmedetomidine 1μg/kg in 50mI normal saline over a period of 10 minutes after induction and before PNP, followed by a continuous infusion at the rate of 0.5 ml/kg/hr. (0.2 μg/kg/hr).

DATA COLLECTION

Preanesthetic assessment of all the selected patients were done with complete history, general examination, airway assessment, systemic examination along with laboratory investigations (complete blood count, random blood sugar, kidney function test including serum electrolytes [Na+, K+], liver Function Test [AST, ALT, ALP], urine [Routine &Microscopic], chest X-ray PA view and electrocardiogram).

During perioperative period, hemodynamic parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded various intervals [0 minute (Base value), D0 (Before study drug/immediate after intubation),D10 (After study drug), BPN (Beforepneumoperitoneum), APN for various intervals (after creation of pneumoperitoneum), RPN (Release of pneumoperitoneum), and AR (after reversal)].

Patients were closely observed for bradycardia or tachycardia (± 20% of basal value), hypotension/hypertension (± 20% of basal value), bradyarrhythmia and desaturation (<85%) during intra and postoperative period. During postoperative period along with above, nausea, vomiting,Respiratory depression, sedation and shivering were also recorded if occurred. Any complication if occurred was treated with appropriate medications.

STATISTICAL ANALYSIS

Statistical analysis was performed by using chi square test/fisher exact test for categorical data. One way ANOVA test was used for comparing mean value between three groups. Paired t-test was used to test the relative change with respect to time. P-value less than 0.05 considered as significant at 95% confidence level. The statistical software IBM-SPSS version 25.0 was used in the analysis.

RESULTS

In present study the mean age (in years)for the groups A, B and C were 41.13±11.94, 40.70±13.85 and 39.20±14.26 respectively. The mean weight (in kg) for the groups A, B and C were 61.47±12.45, 58.03±9.99 and 63.93±12.50 respectively. In our study, majority of

patients were females in group A, B and C. In present study the mean duration of surgery (in minutes) for the groups A, B and C were 72.43±6.48, 73.40± 6.01 and 73.80±6.01 respectively.In present study the mean duration of pneumoperitoneum (in minutes) for the groups A, B and C were 59.10±3.95, 60.03±3.46 and 60.23±3.65respectively. The baseline characteristics of the three were statistically comparable (p>0.05) (Table 1).

Table 1: Baseline characteristics of the study subjects in three groups

Variables	GROUP A (n=30)	GROUP B (n=30)	GROUP C(n=30)	P value
Age (in years)*	41.13±11.94	40.70±13.85	39.20±14.26	0.897
Weight (in Kg)*	61.47±12.45	58.03±9.99	63.93±12.50	0.242
Gender#				
Male (n=28)	08 (28.6)	10 (35.7)	10 (35.7)	0.812
Female (n=62)	22 (35.4)	20 (32.3)	20 (32.3)	
Surgery duration (in min)*	72.43±6.48	73.40±6.01	73.80±6.01	0.679
Duration of pneumoperitoneum (in min)*	59.10±3.95	60.03±3.46	60.23±3.65	0.451
RSSS	1.37±0.61	1.67±0.88	2.10±0.99	0.005

The mean HR (bpm) before induction in group A, B, and C was 87.30 ±12.31, 84.97±8.05 and 81.03±4.60 respectively.On comparing with the baseline values in group A, there was increase in HR to101.97±12.34 bpm immediately after intubation.Monitoring of mean HR to 15 minutes after reversal showed decrease in values to 89.77±7.13bpm. In group B, immediately after creation of PNP, HR increased to 95.47±10.33 bpm which came down towards theAPN10(86.47±7.80 bpm), APN30 (86.8±7.78 bpm), and APN90 (88.20±5.49 bpm). After infusion of loading dose of dexmedetomidine significant fall in mean HR was seen (±2.55 bpm) which remained similar to baseline values after creation of PNP (83.83±3.56 bpm). In group C, there was a slight increase in mean HR after reversal (94.73±9.18 bpm) which was similar to baseline value, after which HR decreased to 83.20±3.71 bpm, 15 min after reversal (Table 2).

Table 2: Comparison of heart rate during perioperative period among subjects in three groups

Variables	GROUP A (n=30)	GROUP B (n=30)	GROUP C (n=30)	P value
HR B	87.30±12.31	84.97±8.05	81.03±4.60	0.026
HR DO	101.97±12.34	95.47±10.33	94.73±9.17	0.019
HR D10	90.30±11.36	86.47±7.79	82.57±6.99	0.005
HR BPN	89.07±10.75	86.47±7.80	82.27±5.93	0.009
HR APN	98.83±10.75	95.47±10.33	84.97±8.05	<0.0001
HR APN 10	88.60±9.98	86.47±7.80	82.27±5.93	0.011
HR APN 20	88.43±9.74	87.80±5.87	82.27±5.93	0.003
HR APN 30	88.60±9.98	86.80±7.78	82.27±5.93	0.010
HR APN 40	90.00±8.35	87.87±6.30	82.67±5.36	<0.0001
HR APN 50	90.37±7.89	88.20±5.48	83.20±3.71	<0.0001
HR APN 90	89.77±7.13	88.20±5.49	83.20±3.71	<0.0001
HR RPN	98.83±10.75	95.47±10.33	84.17±7.62	<0.0001
HR AR	102.50±10.39	95.87±9.60	94.73±9.18	0.005

HR AR 15	89.77±7.13	88.20±5.48	83.20±3.71	<0.0001

The mean SBP (mmHg) before induction in group A, B, and C was 126.0±10.92, 119.40±6.50, and 122.13±4.87 respectively. In group A, during whole PNP, no significant changes in SBP were observed as shown by values APN10 (122.13±4.87 mmHg), APN30 (122.57±7.05 mmHg), and APN50 (123.23±6.58 mmHg) (p>0.05). In group B, the release of PNP, SBP increased to 126.00±10.92, 119.40±6.50, and 122.13±4.87 mmHg followed by another rise in SBP after the reversal (119.97± 8.26) which decreased to 119.97±8.26 mmHg, 15 minutes after reversal. In group C, a significant fall in SBP was found after infusion of loading dose of dexmedetomidine (118.10±4.68 mmHg)which remained lower even after creation of PNP(124.67±9.89 mmHg) (Table 3).

Table 3: Comparison of systolic blood pressure during perioperative period among subjects in three groups

Variables	GROUP A (n=30)	GROUP B (n=30)	GROUP C (n=30)	P value
SBP B	126.00±10.92	119.40±6.50	124.67±9.89	0.018
SBP DO	136.67±8.51	133.60±8.86	140.07±4.53	0.006
SBP D10	124.73±7.51	118.10±4.68	119.90±8.34	0.001
SBP BPN	124.87±7.00	117.37±4.69	119.97±8.26	<0.0001
SBP APN	131.13±7.46	123.00±5.89	124.67±9.89	<0.0001
SBP APN 10	122.13±4.87	119.96±8.26	117.37±4.69	0.014
SBP APN 20	119.97±8.26	117.37±4.69	115.00±4.22	0.008
SBP APN 30	122.57±7.05	117.37±4.69	115.00±4.22	<0.0001
SBP APN 40	123.10±7.01	117.37±4.69	115.00±4.22	<0.0001
SBP APN 50	123.23±6.58	117.10±4.58	115.00±4.22	<0.0001
SBP APN 90	116.73±5.08	116.83±4.61	114.47±3.80	0.078
SBP RPN	133.60±8.86	122.13±4.87	119.97±8.26	<0.0001
SBP AR	134.73±7.58	119.97±8.26	123.23±6.58	<0.0001
SBP AR 15	123.23±6.58	119.97±8.26	117.37±4.69	0.004

The mean DBP (mmHg) before induction in group A, B, and C was 81.40±9.43, 78.53±7.33, and 80.07±7.38respectively.In group A, during whole PNP, no significant changes in DBP were observed as shown by values APN10 (78.33±5.23 mmHg), APN30 (82.00±4.56 mmHg), andAPN50(82.90±3.61 mmHg). In group B, there was increase in DBP after the reversal (83.33±5.42 mmHg) which decreased to 78.13±5.12 mmHg, 15 minutes after reversal. In group C, after the release of PNP,DBP increased to 76.07±3.66 mmHg followed by rise in DBP after the reversal (76.90±5.51 mmHg) which decreased to 77.43±5.92mmHg,15 min after reversal (Table 4).

Table 4: Comparison of diastolic blood pressure during perioperative period among subjects in three groups

Variables	GROUP A (n=30)	GROUP B (n=30)	GROUP C (n=30)	P value
DBP B	81.40±9.43	78.53±7.33	80.07±7.38	0.395
DBP DO	88.47±5.29	84.60±3.50	80.60±7.20	<0.0001
DBP D10	83.33±5.42	76.90±5.51	74.57±4.92	<0.0001
DBP BPN	82.00±4.56	76.83±5.41	74.57±4.92	<0.0001

DBP APN	87.43±4.38	78.33±5.23	77.43±5.92	<0.0001
DBP APN 10	78.33±5.23	77.43±5.92	74.57±4.92	0.021
DBP APN 20	78.33±5.23	75.53±4.38	74.17±4.61	0.004
DBP APN 30	82.00±4.56	75.53±4.38	74.17±4.61	<0.0001
DBP APN 40	82.00±4.56	75.53±4.38	74.17±4.61	<0.0001
DBP APN 50	82.90±3.61	75.80±4.01	74.57±4.39	<0.0001
DBP APN 90	78.33±5.23	75.53±4.38	74.17±4.61	0.004
DBP RPN	83.33±5.42	76.90±5.51	76.07±3.66	<0.0001
DBP AR	88.47±5.3	83.33±5.42	76.90±5.51	<0.0001
DBP AR 15	76.90±5.51	78.13±5.12	77.43±5.92	0.688

The mean MAP (mmHg) before induction in group A, B, and C was 91.57±5.49, 91.57±5.49, and 96.20±4.82 respectively. In group A, during whole PNP, insignificant changes in MAP were observed as shown by values APN10 (91.57±5.49 mmHg), APN30 (96.50±4.53mmHg), and APN50(97.67±4.68 mmHg). In group B, after the release of PNP, MAP increased to 96.20±4.82mmHg and remained significantly elevated after the reversal (101.67±4.69 mmHg) which gradually decreased to 94.17±6.01 mmHg 15 minutes after reversal. In group C, during the whole PNP, fall in MAP were observed as shown by values APN10(87.60±5.10 mmHg), APN30 (87.40±3.67 mmHg) and APN50 (86.90±3.47 mmHg) (Table 5).

Table 5: Comparison of meanarterial pressure during perioperative period among subjects in three groups

Variables	GROUP A (n=30)	GROUP B (n=30)	GROUP C (n=30)	P value
MAP B	96.50±4.53	91.57±5.49	96.20±4.82	<0.0001
MAP DO	106.13±2.70	106.53±2.19	105.57±3.29	0.401
MAP D10	96.50±4.53	88.37±4.51	86.90±5.54	<0.0001
MAP BPN	96.50±4.53	88.57±4.34	87.60±5.10	<0.0001
MAP APN	104.37±2.44	91.57±5.49	96.20±4.82	<0.0001
MAP APN 10	91.57±5.49	88.37±4.51	87.60±5.10	0.007
MAP APN 20	91.63±5.25	87.40±3.67	85.80±4.23	<0.0001
MAP APN 30	96.50±4.53	89.73±4.78	87.40±3.67	<0.0001
MAP APN 40	95.47±4.26	89.30±4.88	87.40±3.67	<0.0001
MAP APN 50	97.67±4.68	91.77±5.70	86.90±3.47	<0.0001
MAP APN 90	91.27±4.70	86.90±3.53	85.13±3.56	<0.0001
MAP RPN	102.00±3.46	96.20±4.82	92.90±6.62	<0.0001
MAP AR	106.13±2.70	101.67±4.69	96.10±4.81	<0.0001
MAP AR 15	97.67±4.68	94.17±6.01	91.77±5.70	<0.0001

The sedation score in group A, B, and C was 1.37±0.61, 1.67±0.88 and 2.10±0.99 respectively and the difference in the three groups was statistically significant (p<0.05).

DISCUSSION

In present study, on comparing with the baseline values in control group, there was increase in HR to 101.97±12.34 bpm immediately after intubation. Monitoring of mean HR to 15

minutes after reversal showed decrease in values to 89.77±7.13bpm. In clonidine group, immediately after creation of PNP, HR increased to 95.47±10.33 bpm which came down towards the APN10(86.47±7.80 bpm), APN30 (86.8±7.78 bpm), and APN90 (88.20±5.49 bpm). After infusion of loading dose of dexmedetomidine significant fall in mean HR was seen (±2.55 bpm) which remained similar to baseline values after creation of PNP (83.83±3.56 bpm). In dexmedetomidine group, there was a slight increase in mean HR after reversal (94.73±9.18 bpm) which was similar to baseline value, after which HR decreased to 83.20±3.71 bpm, 15 min after reversal.

Joris et al., observed the similar results with the use of clonidine as a premedication in a dose of 8µg/kg [8].Kalra et al., used clonidine 1µg/kg iv over a period of 15 minutes before pneumoperitoneum and observed significantly better hemodynamic control than control group [12].Roy et al compared intravenous clonidine (2.25µg/kg bolus and 0.9µg/kg/hr. infusion) and IV lignocaine (1.5µg/kg bolus and 0.6µg/kg/hr. infusion) in laparoscopic hysterectomy and attenuation in heart rate was significantly more in clonidine group [13].

Hazra et al., observed the similar results with administered of IV clonidine 1µg/kg, IV dexmedetomidine 1µg/kg and normal saline in three different groups, 15 minutes prior to induction. There was significant reduction in mean heart rate at various intervals during pneumoperitoneum. These findings are very similar to our study which stated that dexmedetomidine provides better heart rate control as compared to clonidine and control group in laparoscopic surgeries [14].

Bhattacharjee et al., observed the similar results with the use of dexmedetomidine at an infusion rate of 0.2µg/kg/hr. and observed that heart rate decreased significantly after intubation and pneumoperitoneum and remained lower throughout the pneumoperitoneum in comparison to control group (p<0.01) [15].

In present study, on comparing dexmedetomidine group with clonidine group, insignificant fall (p>0.05) in DBP were observed at all intervals except at 30 minutes after pneumoperitoneum (APN30) and after reversal(DBP_AR).While comparing Dexmedetomidine group with clonidine group, insignificant fall (p>0.05) in SBP and MAP were observed at all intervals except at 50 minutes after pneumoperitoneum (APN50).

Hazraet al., compared clonidine 1 µg/kg iv and dexmedetomidine 1µg/kg iv and observed no significant difference in SBP,DBP and MAP in both groups while controlling stress response during pneumoperitoneum, whereas both drugs were effective in attenuating hemodynamic changes of pneumoperitoneum. Our finding was similar to these observations [13].

Joris et al., observed that pneumoperitoneum results in an increase in MAP, SVR, PVR and decrease in cardiac output. The increase in SVR was associated with marked release of vasopressin and catecholamines.Clonidine (8µg/kg) given before pneumoperitoneum reduced the release of catecholamine's and thus significantly attenuated the increase in MAP and heart rate in comparison to placebo [16].

Passiet al., observed that with oral clonidine(150µg) premedication 60-90 minutes before laparoscopy, change in MAP was significantly lower and MAP varied between 88±9 to 95±9 mmHg as compared to control group (vit B complex tablets) in which MAP varied between 97±14 to106±5 mmHg [17].

Studies by Gupta et al., Bhandari et al., Yu et al., Sung et al., and Chandrashekariah et al., also observed similar findings [18,19,20,21,22].

In present study mean sedation score after extubation was measured using Ramsay sedation score. The sedation score in group A, B, and C was 1.37±0.61, 1.67±0.88 and 2.10±0.99 respectively and the difference in the three groups was statistically significant (p<0.05).Similar results were found in study done by Kumar et al., they found that dexmedetomidine provided longer duration of analgesia and significantly higher sedation than clonidine [23].

CONCLUSION

Creation of pneumoperitoneum in laparoscopic abdominal surgeries produces significant increase of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP).During pneumoperitoneum in laparoscopic abdominal surgeries both intravenous clonidine and intravenous dexmedetomidine results to attenuate in all hemodynamic parameters (HR, SBP, DBP and MAP)During pneumoperitoneum in laparoscopic surgeries heart rate is better controlled bydexmedetomidine.However, dexmedetomidine and clonidine are equally effective for controlling blood pressure.Both the drugs have no respiratory complications seen but dexmedetomidine produces higher sedation as compared to clonidine.No complications were observed with both study drugs.

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