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Intravenous paracetamol versus dexmedetomidine in patients undergoing laparoscopic cholecystectomy: hemodynamic changes

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Abstract

In laparoscopic surgeries, marked hemodynamic changes occur due to the effect of absorption, positioning of the patient, anesthetic agents and pneumoperitoneum. When the intra-abdominal pressure is < 10mmHg, hemodynamic alteration is not significant. Significant alteration in hemodynamics occurs, when the intra-abdominal pressure is > 10 mmHg after insufflation. When the intra-abdominal pressure is >10mmhg, it will cause inferior vena cava compression and pooling of blood in the lower extremities, which decreases the venous return to the heart thereby reducing the cardiac output. On receiving patient in operating room, the patient monitoring included electrocardiogram (ECG), noninvasive blood pressure (NIBP), heart rate (HR), oxygen saturation (SPO_2). The baseline HR, NIBP, SpO_2 scores were recorded. The hemodynamic parameters taken into consideration were the heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure. Mean values of these parameters were analyzed from the baseline, every minute for the first 10 min thereafter for every 5 min till the end of surgery. The heart rate was significantly lower in dexmedetomidine group during the initial 10 min during infusion, lowest mean of 79.53±13.08, none of the patients from either group had bradycardia requiring atropine. Mean value of HR was higher in paracetamol group compared to dexmedetomidine group till 1 h postoperatively. Using preanesthetic dexmedetomidine 1µg/kg infusion followed by 0.5 µg/kg/h showed there was no difference in MAP between the groups, but heart rate of dexmedetomidine group was lower compared to the control group.

Keywords: Intravenous paracetamol, dexmedetomidine, hemodynamic changes

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Introduction

Laparoscopic surgeries are minimal invasive surgeries in which inert gas is insufflated into the abdomen to diagnose and operate. It is used in gastrointestinal, urological, gynecological, and vascular surgeries [1].
Creation of pneumoperitoneum and altered patient position in laparoscopic surgeries predispose to certain pathophysiological changes.
In laparoscopic surgeries, marked hemodynamic changes occur due to the effect of absorption, positioning of the patient, anesthetic agents and pneumoperitoneum. When the intra-abdominal pressure is < 10mmHg, hemodynamic alteration is not significant. Significant alteration in hemodynamics occurs, when the intra-abdominal pressure is > 10 mmHg after insufflation. When the intra-abdominal pressure is >10mmhg, it will cause inferior vena cava compression and pooling of blood in the lower extremities, which decreases the venous return to the heart thereby reducing the cardiac output. Degree of change in cardiac output depends upon the change in the intra-abdominal pressure. Increase in intra-abdominal pressure also increases intra thoracic pressure, which increases the peripheral vascular resistance [2]. Mechanical stimulation of peritoneal receptor releases catecholamines and vasopressin, which contributes to increase in the peripheral vascular resistance. Arrhythmias including bradycardia and a systole can also occur during laparoscopy due to sudden stretching of the peritoneum by stimulating the vagus nerve.

Neuroendocrine effects: Laparoscopic approach to cholecystectomy results in attenuation of acute phase reaction, leading to reduced levels of C-reactive protein (CRP) and interleukin -6 (IL-6) when compared to open technique. Laparoscopic technique also results in a decreased metabolic response (hyperglycemia, leukocytosis), hence leading to an improved immune function and nitrogen balance [3]. Prolonged exposure and manipulation of intestines and peritoneal incision and trauma are avoided by laparoscopic approach to cholecystectomy, thereby reducing postoperative ileus and fasting, duration of intravenous infusion and hospital stay. Endocrine response to surgery does not differ significantly between laparoscopic and open techniques for cholecystectomy, resulting in similar levels of plasma and urinary concentrations of catecholamines and their metabolites in both the techniques. Peritoneal stretching leading to pain and discomfort, hemodynamic alterations and ventilator changes caused by CO_2 insufflation may contribute to the stress response induced by laparoscopy, which can be reduced by perioperative administration of $\alpha 2$ agonists [4].
Pneumoperitoneum decreases the renal blood flow and glomerular filtration (GFR) which leads to decrease in urine output. Renal blood flow increases after deflating the abdomen.
Raised IAP will cause decrease in cerebral perfusion pressure and increase the intracranial pressure [5].

Splanchnic and hepatic blood-flow: The effect of pneumoperitoneum on splanchnic and hepatic blood-flow is unclear. Animal studies suggest that while hypercapnia has a vasodilatory effect, this is opposed by the vasoconstricting effect of the raised intra-abdominal pressure [6].

Methodology

Patients satisfying the inclusion criteria were selected during the study period from the operation register on a daily basis. After obtaining a written informed consent, sixty patients were recruited for this study. They were allocated into two groups of 30 each. Preoperatively, the patients were made familiar of their role in the study and the use of 10 cm VAS with end point to be labeled as 0 = no pain and 10 = excruciating worst possible pain.
On receiving patient in operating room, the patient monitoring included electrocardiogram

(ECG), noninvasive blood pressure (NIBP), heart rate (HR), oxygen saturation (SPO_2). The baseline HR, NIBP, SpO_2 scores were recorded.
Computer based randomization was done and allocation concealment was done by sealed envelope method. An anesthesiologist not involved in the management of the case opened a sealed envelope randomly and loaded drugs as per the drugs in the envelope:

D group:
1) Dexmedetomidine 1µg/kg in 100 ml normal saline and connected to an infusion pump.
2) Dexmedetomidine 2µg/ml in 50 ml normal saline and connected to a syringe pump.

P group:
1) Paracetamol 1g in 100 ml normal saline and connected to an infusion pump.
2) Normal saline in a 50 ml syringe and connected to a syringe pump.

The anesthesiologist in the theatre was blinded to the test drug conducted in the intraoperative anesthetic management and monitoring.
Group D (Dexmedetomidine)-received dexmedetomidine 1µg/kg in 100 ml of normal saline through infusion pump over 10 min. This was followed by an infusion of dexmedetomidine through syringe pump at 0.25ml/kg/h (0.25ml = 0.5µg) of prepared concentration.
Group P (Paracetamol)-received 1 g paracetamol in 100ml solution through infusion pump over 10 min. This was followed by an infusion of normal saline administered through syringe pump at 0.25ml/kg/h.
Vitals were recorded during the infusion for every minute for first 10 min during loading dose. After 10 min, the maintenance dose was started and Preoxygenation was done for 3 minutes with 100% oxygen at 8 L/minute. Inj. IV glycopyrrolate (0.005mg/kg), injection ondansetron 0.1 mg/kg and midazolam 0.02 mg/kg were given as premedication. All patients received propofol 2mg/kg and fentanyl 1 µg/kg followed by atracurium 0.5mg/kg to facilitate tracheal intubation. Anesthesia was maintained with Isoflurane 1% until tracheal intubation. Three minutes later, laryngoscopy was done and oral endotracheal intubation was performed using appropriate size endotracheal tube. Correct placement of endotracheal tube was confirmed by end tidal CO_2 and auscultation.
All patients were mechanically ventilated with fresh gas flow of 2L/min (N_2O:O_2=1:1), FiO_2-50% with minute volume adjusted to maintain $ETCO_2$ between 30-35mmHg using circle absorber breathing system.
During surgery, intraabdominal pressure was maintained at 12-15 mmHg. Heart rate, systolic BP, diastolic BP, mean arterial pressure, oxygen saturation was monitored at baseline, and every 5 min till the end of surgery. After skin closure, the study drugs and all anesthetics were discontinued. Patients were ventilated with 6L/minute Oxygen. Neuromuscular blockade was reversed with neostigmine 50 µg/kg and glycopyrrolate 10µg/kg. Extubation was done once the patients fulfilled subjective and objective criteria for extubation i.e., following commands, intact gag, tidal volume at least 6 ml/kg. The total duration of surgery was observed and recorded.
All patients are kept in the PACU for 2 hrs. HR, blood pressure, SpO_2 and VAS were observed and recorded at 1, 2, 4, 12 and 24 hrs. When the VAS score >3, patients of both groups received IV tramadol 1.5mg/kg. The following parameters are observed: quality and duration of analgesia, hemodynamic parameters and time to first dose of rescue analgesia in 24 h, any postoperative complication or side effects.

Results

The hemodynamic parameters taken into consideration were the heart rate, systolic blood

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pressure, diastolic blood pressure, mean arterial blood pressure. Mean values of these parameters were analyzed from the baseline, every minute for the first 10 min thereafter for every 5 min till the end of surgery.

The results were compared between the groups. Complications like hypotension requiring use of ephedrine (3mg boluses) and bradycardia requiring atropine (0.6 mg) were noted.

The heart rate was significantly lower in dexmedetomidine group during the initial 10 min during infusion, lowest mean of 79.53±13.08, none of the patients from either group had bradycardia requiring atropine. Mean value of HR was higher in paracetamol group compared to dexmedetomidine group till 1 h postoperatively.

Table 1: Comparison of mean heart rate (HR) between the groups

Heart rate (per min)	Group D	Group P	P value
Baseline	90.13±15.13	95.9±15.66	0.152
1 min	88.23±15.98	94.7±13.95	0.100
2 min	85.83±13.81	94.2±13.16	0.020*
3 min	84.13±12.97	93.23±13.86	0.011*
4 min	81.87±12.38	93.1±14.35	0.002**
5 min	81.47±12.71	94.6±15.95	<0.001**
6 min	80.27±12.98	94.13±15.76	0.000
7 min	80.87±13.06	93.57±16.09	<0.001**
8 min	79.77±13.02	94.07±14.87	<0.001**
9 min	79.53±13.08	92.3±15.4	<0.001**
10 min	81.63±15.54	92.43±16.69	0.012*
15 min	83.93±17.08	93.53±18.59	0.042*
20 min	81.73±16.22	92.17±18.01	0.022*
25 min	80.5±16.91	92.8±17.3	0.007**
30 min	81±16.85	94.6±16.76	0.003**
35 min	84.53±17.41	94.5±19.04	0.039*
40 min	84.3±15.99	92.43±16.17	0.055*
45 min	84±15.07	92.3±13.17	0.027*
50 min	81.97±14.47	89.83±14.59	0.040*
55 min	81.47±13.94	90.83±15.81	0.018*
60 min	81.97±14.1	89.57±16.17	0.063+
65 min	80.45±13.89	88.71±15.21	0.036*
70 min	78.59±13.02	87.3±16.11	0.030*
75 min	77.89±12.93	87.41±15.59	0.017*
80 min	78.96±14.7	85.35±16.06	0.149
85 min	77.75±15.58	85.83±13.93	0.068+
90 min	78.09±17.3	86.13±15.93	0.108
95 min	74.5±13.52	87.18±16.73	0.011*
100 min	73.21±14.61	84.78±13.86	0.029*
105 min	70.46±13.64	88.82±14.45	<0.001**
110 min	72.85±17.1	86.69±13.63	0.032*
115 min	74.2±20.05	77.13±9.34	0.710
120 min	73.78±20.43	78.86±8.41	0.549
125 min	84±43.41	77.86±8.51	0.708
130 min	135±0	78.29±8.42	<0.001**
Postoperative at 15 min	78.47±8.11	84.27±8.48	0.009**
Postoperative at 30 min	77.5±7.7	83.67±7.76	0.003**
Postoperative at 45 min	77.83±8.[37]	82.77±7.85	0.022*
Postoperative at 60 min	78.13±8.39	82.8±10.04	0.056
Postoperative at 2 hrs.	84.1±9	82.4±8.5	0.455

Postoperative at 4 hrs.	85.97±8.54	87.17±11.3	0.644
Postoperative at 12 hrs.	86.73±8.42	86.97±10.15	0.923
Postoperative at 24 hrs.	89.7±8.27	87.93±9.21	0.437

Table 2: Comparison of SBP between the groups

Systolic Blood Pressure	Group D	Group P	P Value
Baseline	118.37±24.63	122.57±10.82	0.396
1 Min	117.43±14.49	121.5±13.82	0.271
2 Min	114.33±15.51	122.17±11.55	0.030*
3 Min	113.2±13.32	122.5±13.18	0.009**
4 Min	111.6±12.34	122.43±14.39	<0.001**
5 Min	112.57±12.93	123.4±15.06	<0.001**
6 Min	110.53±13.08	122.17±13.65	<0.001**
7 Min	111.53±13.43	120.4±14.51	0.017*
8 Min	110.53±12.69	122.77±11.92	<0.001**
9 Min	110.43±11.16	121.2±13.18	<0.001**
10 Min	115.9±15.37	122.97±15.88	0.085
15 Min	110.03±15.39	123.33±17.72	<0.001**
20 Min	109.57±22.08	117.57±19.99	0.147
25 Min	106.33±13.03	118.8±18.08	0.003**
30 Min	108.87±16.41	121±17.35	0.007**
35 Min	110.73±15.24	125.17±16.22	<0.001**
40 Min	111.7±14.28	125.07±16.15	<0.001**
45 Min	115.53±15.44	123.33±16.57	0.064+
50 Min	110.7±17.18	125.77±15.42	<0.001**
55 Min	111.9±15.87	121.97±16.57	0.019*
60 Min	109.21±15.64	118.66±17.49	0.034*
65 Min	111.31±15.8	120.66±16.55	0.032*
70 Min	110.79±16.76	121.5±16.19	0.017*
75 Min	109.04±14.52	119.89±16.52	0.012*
80 Min	108.59±14.09	117.04±19.15	0.079+
85 Min	110.83±15.93	114.83±17.61	0.419
90 Min	109±15.49	118.61±16.17	0.046*
95 Min	112.4±19.18	120.43±19.38	0.190
100 Min	110.64±18.09	118.33±14.06	0.186
105 Min	112.08±17.92	121.35±19.76	0.196
110 Min	111.23±16.01	116.62±10.06	0.315
115 Min	114.8±17.42	114.88±10.15	0.992
120 Min	114.67±12.16	114.71±14.74	0.994
125 Min	122±23.3	117.29±21.68	0.765
130 Min	137±0	115.57±18.16	0.312
Postoperative At 15 Min	113±13.38	119.43±11.39	0.050
Postoperative At 30 Min	114.07±9.59	120.7±11.86	0.021*
Postoperative At 45 Min	114.37±10.67	124±14.6	0.005**
Postoperative At 60 Min	116.37±10.74	120.7±11.41	0.135
Postoperative At 2 H	119.73±13.16	124.73±12.4	0.135
Postoperative At 4 H	124.6±9.02	127.6±14.01	0.328
Postoperative At 12 H	127.47±13.3	126.37±12.78	0.745
Postoperative At 24 H	126.63±14.48	126.63±13.56	1.000

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Table 3: Comparison of diastolic blood pressure between the groups

Diastolic Blood Pressure	Group D	Group P	P Value
Baseline	76.27±12.52	74.63±9.38	0.570
1 Min	73.23±11.75	74.33±9.07	0.686
2 Min	70.97±11.67	75.53±8.33	0.086+
3 Min	71.03±10.48	76.07±8.4	0.045*
4 Min	69.9±11.68	74.33±9.45	0.111
5 Min	71.2±12.24	74.67±10.14	0.237
6 Min	69.4±12.06	76±8.75	0.018*
7 Min	68.17±12.26	74.77±9.62	0.024*
8 Min	69.93±14.37	74.8±8.68	0.118
9 Min	71.2±13.97	75.67±8.75	0.143
10 Min	73.33±12.5	73.43±13.54	0.976
15 Min	70.33±14.01	74.5±15.66	0.282
20 Min	68.7±16.71	71.33±15.67	0.531
25 Min	66.47±11.3	74.47±13.78	0.017*
30 Min	68.33±13.06	77.17±14.24	0.015*
35 Min	69.73±14.11	77.9±15.23	0.035*
40 Min	70.5±13.29	80.17±14.32	0.009**
45 Min	72.73±13.07	77.13±12.93	0.195
50 Min	68.6±14.07	76.1±12.72	0.034*
55 Min	70.5±12.23	77.1±13.79	0.055+
60 Min	69.72±14.45	73.97±13.36	0.251
65 Min	69.34±14.23	73.03±13.04	0.308
70 Min	70.66±15.46	73.54±11.88	0.435
75 Min	68.79±12.76	72.5±13.86	0.301
80 Min	69±12.88	70.43±14.85	0.716
85 Min	68.67±12.26	72.39±16.12	0.376
90 Min	68.7±10.53	71.78±14.49	0.413
95 Min	71.15±15.24	72.48±14.3	0.775
100 Min	70.29±12.23	71.89±13.42	0.730
105 Min	72±11.82	74±17.75	0.729
110 Min	69.54±12.89	70.15±10.81	0.896
115 Min	70.1±6.49	69.25±12.48	0.854
120 Min	69.33±6.42	69.86±11.5	0.909
125 Min	76.67±17.24	73.43±13.84	0.759
130 Min	78±0	74.14±12.58	0.784
Postoperative At 15 Min	73.07±7.5	72.43±7.73	0.748
Postoperative At 30 Min	73.2±6.49	72.33±7.48	0.634
Postoperative At 45 Min	74.9±5.89	76.83±8.68	0.317
Postoperative At 60 Min	73.2±6.75	74.87±8.34	0.399
Postoperative At 2 H	77.37±8.59	75.7±8.99	0.466
Postoperative At 4 H	79.03±8.01	79.53±8.32	0.813
Postoperative At 12 H	78.07±8.78	76.83±6.7	0.543
Postoperative At 24 H	79.6±7.99	76.17±7.69	0.095+

There was fall in mean arterial blood pressure in group D in initial 10 min after infusion with p value 0.001 which was statistically significant. No other significant differences in the intraoperative & post-operative hemodynamic parameters of MAP were seen as in the table.

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Table 4: Comparison of mean arterial blood pressure between the groups.

Mean Arterial Pressure	Group D	Group P	P Value
Baseline	89.7±10.34	91.61±8.85	0.445
1 Min	86.5±10.22	91.09±9.86	0.082+
2 Min	84.03±11.01	92.12±8.35	0.002**
3 Min	84.2±8.85	92.61±9.26	<0.001**
4 Min	83.17±8.48	91.48±10.27	<0.001**
5 Min	84.57±9.09	92.06±10.75	0.005**
6 Min	82.57±9.96	92.43±9.32	<0.001**
7 Min	82.6±9.81	90.4±10.75	0.005**
8 Min	81.93±8.44	91.94±8.48	<0.001**
9 Min	82.47±9.22	91.59±9.77	<0.001**
10 Min	89±13.38	91.83±12.44	0.399
15 Min	83.97±13.1	93.87±25.21	0.061+
20 Min	83.03±17.71	88.2±18.59	0.275
25 Min	79.73±11.02	88.13±13.67	0.011*
30 Min	82.2±14.63	91.6±15.2	0.018*
35 Min	83±13.69	94.47±14.27	0.002**
40 Min	84.47±14.67	95.23±15.02	0.007**
45 Min	86.7±13.89	92.37±13.26	0.112
50 Min	82.03±14.54	92.33±13.95	0.007**
55 Min	84.53±14.22	91.17±17.14	0.108
60 Min	83.41±16.15	88.97±15.55	0.184
65 Min	82.9±15.11	89.87±13.98	0.071+
70 Min	84.41±17.2	89.34±12.72	0.220
75 Min	81.86±12.64	88.38±14.57	0.077+
80 Min	82±13.27	85.96±16.01	0.339
85 Min	83±12.02	86.46±18.16	0.441
90 Min	82.13±11.37	87.29±14.53	0.183
95 Min	84.5±16.05	89±14.41	0.344
100 Min	84.79±13.63	85.84±13.25	0.824
105 Min	87.08±13.08	89.72±17.91	0.655
110 Min	84.23±13.82	86.21±10.74	0.679
115 Min	86.3±10.45	85.33±10.05	0.840
120 Min	85.67±8.28	86.13±11.67	0.926
125 Min	93±21	88.86±16.83	0.747
130 Min	101±0	85.57±17.55	0.442
Postoperative At 15 Min	85.37±7.64	89.13±7.84	0.065+
Postoperative At 30 Min	88.23±6.21	90.87±7.09	0.131
Postoperative At 45 Min	89.07±5.24	94.57±9.25	0.006**
Postoperative At 60 Min	89.5±7.2	91.6±8.23	0.297
Postoperative At 2 H	93±9.18	93.87±9	0.713
Postoperative At 4 H	94.63±6.32	96.03±10.23	0.526
Postoperative At 12 H	95.23±9.23	94.03±7.47	0.582
Postoperative At 24 H	95.77±9.5	94±8.83	0.459

Discussion

Dexmedetomidine's special properties favor its use in recovery room. In addition to its sympatholytic effects, analgesic effects and decreased rate of shivering, the preservation of respiratory function allows the continuation of the dexmedetomidine infusion in the extubated, spontaneously breathing patient. The possibility of on-going sedation and sympathetic block could be beneficial in reducing high rates of early postoperative ischemic

events in high-risk patients undergoing non-cardiac surgery. Perioperative administration of dexmedetomidine could be beneficial in chronic opioid users and alcoholics, in high-risk patients as well as in cardiac patients with good to moderately decreased left ventricular function [7].

The quality of sedation produced by dexmedetomidine is different from that produced by other sedatives acting through the GABA (Gamma Amino Butyric Acid) systems. They act through the endogenous sleep promoting pathways. Patients have been described as being very easy to wake up and having the ability to follow commands and coperate while being intubated. Despite sound levels of sedation, there is limited respiratory depression, providing wide safety margins [8].

The primary site of analgesic action is thought to be the spinal cord. It is also shown to have an analgesic effect when injected via the intrathecal or epidural route. Dexmedetomidine also inhibits the release of substance P from the dorsal horn of the spinal cord, leading to primary analgesic effects [9].

Dexmedetomidine in animal models of incomplete cerebral ischemia and reperfusion reduces cerebral necrosis and improves neurologic outcome. It is shown to reduce the intracerebral catecholamine outflow during injury resulting in less neural tissue damage with better neurologic outcome.

Dexmedetomidine effect on respiration appears to be similar in order of magnitude to those seen in the heavy sleep state. Dexmedetomidine does not suppress respiratory function, even at high doses. It has no adverse effects on respiratory rate and gas exchange when used in spontaneously breathing ICU patients after surgery. It helps in maintaining sedation without respiratory drive depression and hence may facilitate weaning and extubation in trauma/surgical ICU patients who have failed previous attempts at weaning because of agitation and hyperdynamic cardiopulmonary response [10].

Dexmedetomidine in animal studies has demonstrated the occurrence of natriuresis and diuresis. It has shown to cause diuresis and natriuresis, possibly through its ability to reduce efferent sympathetic outflow of the renal nerve. It decreases the secretion of vasopressin and increases the release of atrial natriuretic peptide [16].

Action of dexmedetomidine on endocrine system is mainly related to its action on sympathetic outflow and the decrease of catecholamines. This attenuates the responses to stress by inhibiting the secretion of adrenocorticotropic hormone (ACTH) and cortisol. In addition, stimulation of α2 adrenoceptor agonists located on cells of the Islet of Langerhans can temporally cause direct inhibition of insulin release with concomitant detectable clinical hyperglycemia [11]. Dexmedetomidine is an imidazole agent but unlike etomidate, it does not appear to inhibit steroidogenesis when used as an infusion for short-term sedation [12].

Conclusion

Using preanesthetic dexmedetomidine 1µg/kg infusion followed by 0.5 µg/kg/h showed there was no difference in MAP between the groups, but heart rate of dexmedetomidine group was lower compared to the control group.

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