Original Article

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Effects of Dexmedetomidine on Intraoperative Hemodynamics and Opioid Requirement in Laparoscopic Cholecystectomy

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Abstract

Introduction: Laparoscopic surgery poses a challenge to its successful anesthetic management due to its significant alteration of hemodynamics resulting from pneumoperitoneum. Dexmedetomidine although frequently used in laparoscopic surgeries produces sedation, analgesia and anxiolysis, alongwith decreasing heart rate and blood pressure. We intended this study to use a lower loading dose of 0.6 μg/kg and maintenance dose of 0.3 μg/kg/h dexmedetomidine so as to utilize its wonderful properties without causing the adverse effects of hypotension and bradycardia, which are common at its usual loading dose of 1 μg/kg and also to study its opioid sparing effect. *Methodology:* A double blinded randomised placebo controlled trial was conducted on sixty adult patients, ASA grade I or II of either sex, aged 18 to 60 years who underwent elective laparoscopic cholecystectomy. Patients were divided into two groups who received dexmedetomidine and normal saline and intraoperative hemody-namicswere studied at different time-points. *Results:* The two groups were comparable with respect to mean duration of surgery (46.67±4.35 vs 47.43±3.96), mean extubation time (6.77 ± 0.73 vs 7.00 ± 0.58), and response to oral commands (8.59 ± 0.7 vs 8.78 ± 0.72). Mean heart rate and blood pressure variations were significantly lower in dexmedetomidine group at all time-points. Fentanyl requirement and post-operative nausea/vomiting was also significantly less in dexmedetomidine group and none patient had any episode of bradycardia, hypotension or hypertension. *Conclusion:* Dexmedeto-midine 0.6 μg/kg followed by maintenance of 0.3 μg/kg/h provides perioperative hemodynamic stability, facilitates smooth emergence from anesthesia, has opioid sparing properties and reduces post op nausea and vomiting.

Keywords:

Opioid; Dexmedetomidine; Hemodynamics; Laparoscopic Cholecystectomy

Introduction

Laparoscopic surgery poses a challenge to its successful anesthetic management mainly due to its significant alteration of hemodynamics resulting from pneumoperitoneum creation causing increased arterial pressure, systemic vascular resistance, pulmonary vascular resistance and decreased cardiac output. Different drugs have been used to attenuate hemodynamic response in laparoscopic surgery Dexmedetomidine, which was approved by FDA (food and drugs administration) in 1999, has been recently introduced in our country. It is finding a vital place for itself as premedication through intravenous route and also for sedation of patients in intensive care unit. As an adjunct to general anesthesia it has minimum alveolar concentration (MAC) and opiate sparing properties, which helps in decreasing the inhalational anesthetic and opioid requirements by up to 90% which can be used to advantage in situations where high anesthetic concentration is either undesirable or not tolerated. It produces sedation and anxiolysis by binding to alpha-2 receptors in the locus ceruleus, which

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diminishes the release of norepinephrine and inhibits sympathetic activity, thus decreasing heart rate and blood pressure. It produces analgesia by binding to adrenoceptors in the spinal cord. Side effects of dexmedetomidine, such as hypotension and bradycardia, are dose dependent. Administering a loading dose over ten minutes and then infusing the maintenance dose, decreases the incidence of these side effects. We intended this study to use a lower loading dose of 0.6 μg/kg and maintenance dose of 0.3 μg/kg/h dexmedetomidine so as to utilize its wonderful properties and not causing the adverse effects of hypotension and bradycardia which are common at its usual loading dose of 1 μg/ kg[1-3].

Methods

It was double blinded randomized placebo controlled trial approved by the institutional medical ethics committee and sixty patients undergoing laparoscopic cholecystectomy were enrolled to evaluate the efficacy of dexmedetomidine to provide intraoperative hemodynamic stability during laparoscopic cholecystectomy and to study fentanyl sparing effect or adverse effects if any.

Patients of either sex, ASA I and II in the age group 18-60 years were included, excluding the patients who were morbidly obese, pregnant or lactating, hypertensives, on drugs like narcotics, hypnotics, anti-hypertensives, anaemic, ASA III,IV and V, preoperative dysrhythmia, preoperative HR < 60 per min and SBP < 60 mmHg, major organ dysfunction, impaired liver and kidney Function Tests, anticipated difficult intubation and intubation after more than twenty secs or more than one attempt.

A thorough pre- operative evaluation of each patient was done, and written informed consent was taken, and all inclusion and exclusion criteria met. Routine preoperative preparation consisted of fasting 6-8 hours prior to surgery for solids and two hours for liquids was done and all the patients were premedicated with alprazolam 0.5 mg night before the surgery. Basic standard monitoring was done by means of Datex-ohmeda with intellivue MP20 monitor to measure hemodynamics required for the study. Important parameters included HR and rhythm, NIBP, SpO_2, $EtCO_2$, temperature and neuromuscular monitoring at baseline, just after test drug preloading, just before and after intubation,at skin incision, just after insufflation, at 15 min, 30 min, just after exsufflation, just after reversal and extubation.

Patients were divided into two groups, intravenous line secured with ringer lactate drip. Group A received dexmedetomidine preloading 0.6 μg/kg over 10 minutes followed by 0.3 μg/kg/h infusion till removal of scope from the abdominal cavity by the surgeon. Every patient received 100% preoxygenation for three min and fentanyl citrate 2 μg/kg followed by induction with inj propofol (1-2mg/kg iv) infused slowly till absence of eye opening in response to verbal command followed by vecuronium bromide, intubation done after 3 min after Direct laryngoscopy with appropriate size ETT checked by auscultation, maintenance done with 50% O_2 and 50% N_2O and isoflurane to maintain HR and BP within 20% of baseline. Extra requirement of fentanyl citrate (0.5-1μg/kg) was administered depending upon clinical condition (movement, swallowing, lacrimation, sweating and HR, SBP rise by 20% from baseline) and was noted. Extra requirement of vecuronium bromide was done by means of neuromuscular monitoring. Extubation was done after full satisfaction of patient recovery ie ability to open eyes, follow verbal commands, maintain regular breathing pattern.

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. For within the group comparisons, paired *t* test was used to compare variables (Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Pressure) at different time points from baseline. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate, *p* value <0.05 was considered statistically significant.

Results

The two groups were comparable with respect to age, sex, weight, mean duration of surgery (46.67 ± 4.35 min vs 47.43 ± 3.96 min), mean extubation time (6.77 ± 0.73 min vs 7.00 ± 0.58 min), and response to oral commands (8.59 ± 0.7 min vs 8.78 ± 0.72 min).Mean heart rate and blood pressure variations were significantly lower in dexmedetomidine group at all time-points (Tables 1 to 4). Fentanyl requirement and post-operative nausea/vomiting was also significantly less in dexmedetomidine group and none patient had any episode of bradycardia, hypotension or hypertension (Figure 1).

Table 1: Mean Pulse Rates (± SD) at different time – points in both groups (In bpm)

HR	Group A Mean ± SD	Group B Mean ± SD	*p* Value
Baseline(T-ctrl)	80.40 ± 4.25	78.33 ± 6.35	0.440
Just after test dose preloading (T-Load)	67.53 ± 4.22	79.20 ± 6.39	<0.001
Just before intubation (T-Ind)	66.53 ± 3.31	76.13 ± 6.28	<0.001
Just after intubation (T-Int)	69.73 ± 2.72	89.53 ± 7.38	<0.001
At skin incision (T-Inc)	69.03 ± 2.99	90.37 ± 8.67	<0.001
Just after insufflation (T-Ins)	71.27 ± 4.09	93.53 ± 8.27	<0.001
15 min after insufflation(T-Ins15)	70.07 ± 4.09	92.83 ± 8.48	<0.001
30 min after insufflation(T-ins30)	68.33 ± 3.39	81.40 ± 6.66	<0.001
At exsufflation(T-Exs)	72.90 ± 3.73	81.57 ± 6.50	<0.001
Just after reversal(T-Rev)	80.57 ± 5.84	87.40 ± 6.77	<0.001
Just after extubation(T-Ext)	81.47 ± 4.01	86.83 ± 8.40	<0.001

Table 2: Mean SBP (± SD) at different time–points in both groups (mm Hg)

SBP	Group A Mean ± SD	Group B Mean ± SD	*p* Value
Baseline(T-ctrl)	124.13 ± 6.12	121.90 ± 7.42	0.209
Just after test dose preloading (T-Load)	121.10 ± 5.62	121.03 ± 6.77	0.967
Just before intubation (T-Ind)	113.07 ± 6.72	116.67 ± 7.05	0.048
Just after intubation (T-Int)	121.20 ± 5.89	125.30 ± 9.36	0.047
At skin incision (T-Inc)	115.93 ± 6.12	122.00 ± 7.47	0.001
Just after insufflation (T-Ins)	122.03 ± 6.87	132.37 ± 7.18	<0.001
15 min after insufflation(T-Ins15)	120.27 ± 9.00	131.13 ± 8.17	<0.001
30 min after insufflation(T-ins30)	120.73 ± 7.99	130.33 ± 8.34	<0.001
At exsufflation(T-Exs)	119.63 ± 5.83	124.00 ± 7.70	<0.001
Just after reversal(T-Rev)	123.57 ± 5.32	126.23 ± 6.92	0.025
Just after extubation(T-Ext)	125.13 ± 2.18	126.07 ± 8.56	0.264

Table 3: Mean DBP (± SD) at different time–points in both groups (mm Hg)

DBP	Group A Mean ± SD	Group B Mean ± SD	*p* Value
Baseline(T-ctrl)	81.27 ± 4.15	78.90 ± 5.37	0.061
Just after test dose preloading (T-Load)	81.13 ± 7.11	78.33 ± 5.09	0.085
Just before intubation (T-Ind)	73.63 ± 3.94	71.30 ± 4.23	0.031
Just after intubation (T-Int)	79.53 ± 5.76	85.80 ± 5.52	<0.001
At skin incision (T-Inc)	79.23 ± 5.59	83.37 ± 7.12	<0.001
Just after insufflation (T-Ins)	83.63 ± 4.75	88.43 ± 5.49	<0.001
15 min after insufflation(T-Ins15)	82.17 ± 4.68	88.13 ± 6.64	0.049
30 min after insufflation(T-ins30)	80.30 ± 4.65	86.73 ± 6.27	<0.001
At exsufflation(T-Exs)	80.23 ± 4.44	83.57 ± 5.49	0.012
Just after reversal(T-Rev)	79.50 ± 5.64	84.60 ± 6.95	0.001
Just after extubation(T-Ext)	82.13 ± 4.02	83.43 ± 6.73	0.367

Table 4: Average of MAP (± SD) at different time – points in both groups (mm Hg)

MAP	Group A Mean ± SD	Group B Mean ± SD	*p* Value
Baseline(T-ctrl)	95.56 ± 4.39	93.23 ± 5.75	0.084
Just after test dose preloading (T-Load)	94.46 ± 5.12	92.57 ± 2.13	0.159
Just before intubation (T-Ind)	86.78 ± 3.85	86.42 ± 4.00	0.727
Just after intubation (T-Int)	93.42 ± 4.47	98.97 ± 6.08	<0.001
At skin incision (T-Inc)	91.46 ± 5.16	96.24 ± 6.20	<0.001
Just after insufflation (T-Ins)	96.43 ± 4.47	103.08 ± 5.56	<0.001
15 min after insufflation(T-Ins15)	94.87 ± 5.43	102.47 ± 6.47	0.001
30 min after insufflation(T-ins30)	93.78 ± 5.23	101.27 ± 6.41	<0.001
At exsufflation(T-Exs)	93.37 ± 4.20	97.04 ± 5.10	0.015
Just after reversal(T-Rev)	94.19 ± 4.46	98.48 ± 6.32	0.001
Just after extubation(T-Ext)	96.47 ± 5.40	97.64 ± 6.86	0.923

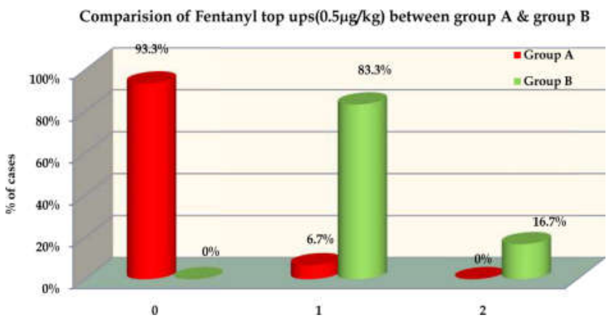

Fig. 1: Comparison of fentanyl top-ups in group A and B

Discussion

The hemodynamic alterations owing to intense sympathetic stimulation accompanying laparoscopic surgery, comprising of elevation of heart rate and rise in systolic, diastolic and mean arterial pressure are well known. Dexmedetomidine, a highly selective α_2-agonist, has been used by many workers like Bhattacharjee DP et al [4], Aantaa R et al [5], YildizM et al [6], Bajwa SS et al [7] etc. for attenuation of hemodynamic responses in various doses and along with various anaesthetic regimens for various types of surgeries.

Bhattacharjee DP et al [4] studied the effects of dexmedetomidine on hemodynamics by using 0.2 µg/kg/h dexmedetomidine and compared with normal saline as control and concluded that dexmedetomidine infusion provides better peri-operative hemodynamics during laparoscopic cholecystectomy.

Laparoscopic cholecystectomy is done in reverse tredelenberg position which diminishes venous return thereby leading to fall in cardiac output. Ishizaki Y et al [8] tried to evaluate the safe intra-abdominal pressure during laparoscopic surgery and observed that hemodynamic alterations were not observed at 12 mm Hg and significant fall in cardiac output was observed at 16 mm Hg of intra-abdominal pressure. Based on all these observations the current recommendation is to monitor intra - abdominal pressure and to keep it as low as possible. In our study, following pneumoperitoneum with carbon dioxide, minute ventilation was adjusted so as to maintain normocapnia. Intra - abdominal pressure (IAP) was monitored throughout the surgery and maintained below 14 mm Hg.

Mean baseline haemodynamic parameters were comparable in both groups. In dexmedetomidine group, there was a statistically significant fall in the mean pulse rate from baseline after the dexmedetomidine pre – loading infusion. This fall in pulse rate can be attributed to the sympatholytic effect of dexmedetomidine. Our study was comparable to study done by Yildiz M et al [6], Ghodki PS et al [9] and Bajwa SS et al [7] who reported that a fall in heart rate after preloading with dexmedetomidine. The mean PR was significantly below baseline at all - time points after induction till exsufflation. It gradually increased after reversal and returned to baseline just after extubation. Such an increase in mean pulse rate after the administration of injection neostigmine and glycopyrrolate for reversal and return to normal values after extubation in dexmedetomidine group was also reported by Bajwa SS et al [7].

Comparison between the two groups revealed that systolic blood pressure was comparable at baseline. Just after induction, systolic BP was lower in dexmedetomidine group which may be attributed to hypotension caused by dexmedetomidine adding to hypotension caused by induction agents. After intubation, systolic BP values in dexmedetomidine group were lower than control at all time-points, difference being significant just after insufflation till just after reversal.

Tufanogullari B et al [10] studied the effect of dexmedetomidine on both early and late recovery after laparoscopic bariatric surgery. Eighty consenting ASA II–III morbidly obese patients were randomly assigned to 1 of 4 treatment groups: (1) control group received a saline infusion during surgery, (2) Dex 0.2 group received an infusion of 0.2µg/kg/hr (3) Dex 0.4 group received an infusion of 0.4µg/kg/hr and (4) Dex 0.8 group received an infusion of 0.8 µg/kg/hr IV. The intraoperative hemodynamic values were similar in the four groups, arterial blood pressure values were significantly reduced in the Dex 0.2, 0.4, and 0.8 groups compared with the control group on admission to the postanaesthesia care unit (PACU).

Comparison between the two groups revealed that the mean diastolic blood pressure was comparable at baseline (p – value > 0.05). Just after induction, DBP in Group A (Test) was lower than in Group B (Control), which may be attributed to the additive effect of dexmedetomidine hypotensive effects with induction agents but none of the patients developed hypotension. After intubation, similar to Systolic BP, Diastolic BP values in Group A (Study) were lower than in Group A (Study) at all time – points, differences being significant at skin incision, just after insufflation, 15 and 30 min of insufflation, exsufflation and at reversal (p - value < 0.05).

Similar to systolic and diastolic BP, when the averages of MAP at different time points were compared in both groups, after induction, MAP decreased further, which may be attributed to additive hypotensive effect of induction agents over sympatholytic effect of dexmedetomidine. This fall in MAP after induction was statistically significant (*p*– value < 0.05). Bhattacharjee DP et al [4], Kang WSet al [11], Kabukcu HK et al [12],Bajwa SS et al [7] and Gupta K et al [13] also found this decrease in MAP after induction to be significant in their respective studies. The average of MAP gradually increased and crossed baseline just after insufflation. After exsufflation, it decreased below baseline, only to increase again after reversal and cross baseline just after extubation. Similar rise – fall – rise trend for MAP was observed by Bhattacharjee DP et al [4] and Gupta K et al [13] in their respective studies, except that MAP remained below baseline at all-time points. Increase in MAP after reversal was also reported in a study by Bajwa SS et al [7]. Kabukcu HK et al [14], in their study, found MAP after intubation to be significantly below baseline. But, no significant difference from baseline was seen at any time point in present study, except just after induction / just before intubation. Yildiz M et al [6] used dexmedetomidine 1µg/kg as a single preinduction dose in one group and the other group received normal saline at same dose, scheduled for elective minor surgeries to see its effect on perioperative hemodynamics. Both groups received fentanyl 1µg/kg during induction. They found that dexmedetomidine group had decreased blood pressure and heart rate as well as the recovery time.

Bhattacharjee DP et al [4] compared infusion of dexmedetomidine 0.2µg/kg/h and normal saline 0.2µg/kg/h in patients undergoing laparoscopic cholecystectomy and found that there was no difference in extubation time and response to oral commands in both the groups and the hemodynamics were much more stable as compared to placebo group during extubation in dexmedetomidine group . These findings were similar to our study results. Mean duration of surgery was comparable in both the groups, haemodynamic parameters at extubation were found to be more stable in dexmedetomidine group.

None of the patients had any episode of bradycardia and hypotension in both the group. Studies using dexmedetomidine have reported cardiovascular side effects such as bradycardia, sinus arrest and hypotension. But none of the patients in our study had such episode owing to probably lower dose of dexmedetomidine 0.6 µg/kg loading followed by 0.3µg/kg/h.

In our study none of the patients in dexmedetomidine group had nausea and vomiting in the post-operative period, whereas four patients in control group had nausea and vomiting. Masad et al [14] reported reduced incidence of nausea and vomiting after combining dexmedtomidine to provide balanced anaesthesia in laparoscopic gynecological surgeries. Tufanogullari B et al [10] also found reduced incidence of post- operative nausea and vomiting in patients receiving dexmedetomidine

In dexmedetomidine group only two patients required single fentanyl top-up whereas 25 patients in control group required single fentanyl top-up and five patients required two fentanyl top-up boluses. Bajwa SS et al [7] in their study showed that dexmedetomidine not only decrease the magnitude of haemodynamic response to intubation, surgery and extubation but also decreased the dose of opioids and isoflurane in achieving adequate analgesia and anaesthesia respectively. The requirement of fentanyl and isoflurane during the surgical period was significantly decreased in patients who received dexmedetomidine pre-operatively

Feld et al [15] showed that dexmedetomidine could be used in place of fentanyl for intraoperative control of blood pressure and heart rate during open gastric bypass Surgery.

Limitations

Study was performed in short duration cases (around 1 hr.) and on small no of patients (30 in each group). More studies are required to establish the efficacy on long duration of surgery and larger number of patients. Moreover study was done in ASA 1 and ASA 2 patients, but the usefulness will be of immense help in high risk cardiac patients.

Conclusion

We conclude from our study that dexmedetomidine infusion in the loading dose of 0.6 µg/kg followed by maintenance dose of 0.3 µg/kg/h reduces the rise in HR, SBP, DBP and MAP associated with creation of pneumoperitoneum during laparoscopic cholecystectomy with fentanyl sparing effect and no adverse side effects of bradycardia, hypotension, respiratory depression or post-operative nausea and vomiting at this dosage and also has sedative, hypnotic and anxiolytic properties. However further studies are required in patients with deranged cardio-respiratory function during laparoscopic surgeries to widen the spectrum of dexmedetomidine use.

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