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Effect of Low Dose of Dexmedetomidine Infusion as an Adjunct in Balanced General Anaesthesia in Laparoscopic Colorectal Surgeries: A Prospective Double Blind Randomized Controlled Study

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Abstract

Addition of dexmedetomidine to the list of anaesthetic drugs during laparoscopic colorectal surgeries plays an important role in enhanced recovery after surgery protocols. Reduction in pain and opioid consumption may decrease the incidence of gastrointestinal side effects, hasten recovery of bowel function and reduce the length of hospital stay. We conducted a randomized double blind placebo controlled clinical comparative study using low dose dexmedetomidine infusion as an adjunct to balanced general anaesthesia in laparoscopic colorectal surgeries. After induction and establishment of mechanical ventilation, the study drug infusion was started as bolus of 1 mcg/kg over 10 min followed by an infusion at the rate of 0.2 mcg/kg/h which was continued for postoperative 12 h or till 24 h after the initiation of the infusion which over is earlier. All patients in group D received intravenous over determined and rest in group P received normal saline as placebo in similar rate. Intravenous dexmedetomidine resulted in better haemodynamic stability both in intraoperative and postoperative period. Low dose Dexmedetomidine infusion as an adjunct to general anaesthesia appears to provide significant perioperative haemodynamic stability in laparoscopic colorectal surgery. However, it has limited analgesic and anti-emetic effects. Further studies are needed to define the optimum dose response relationship of dexmedetomidine.

Keywords: Perioperative dexmedetomidine; Laparoscopic colorectal surgery; Hemodynamics; Intraoperative haemodynamics; Postoperative analgesia

Introduction

After the first successful laparoscopic sigmoidectomy in 1991 paved the way for increasing number of successful laparoscopic colorectal surgeries [1,2]. With advancement in anaesthetic and surgical technologies, patients with advanced age and concurrent illness are also increasingly being subjected to radical colorectal surgeries [1]. However, it is not without its share of problems, disadvantages and risks. Repeated creation of pneumo-peritoneum in colorectal surgery and positional changes lead to an alteration in physiology of various organ systems, specially pulmonary and cardiovascular which may itself contribute for adverse perioperative outcome. Several techniques have been advocated to provide haemodynamic stability during laparoscopic surgical procedures. Intravenous pharmacological interventions with nitroglycerine, labetalol, clonidine and dexmedetomidine are an attractive alternative to combat the haemodynamic fluctuation in laparoscopic procedures [3-6]. Addition of dexmedetomedine to the list of anaesthetic drugs during laparoscopic colorectal surgeries is important in enhanced recovery after surgery protocols. Dexmedetomidine has sedative, analgesic, sympatholytic properties and opioid sparing effect without significant respiratory depressant effects.

Reduction in pain and opioid consumption may decrease the incidence of gastrointestinal side effects, hasten recovery of bowel function and reduce the length of hospital stay [3,4]. We conducted a study using low dose dexmedetomidine infusion on haemodynamic and recovery profile after laparoscopic colorectal surgeries. Secondary outcome were to assess the analgesic, anti-shivering and anti-emetic efficacy of this dose of dexmedetomidine during the post-operative period.

Materials and Methods

Keeping in mind the haemodynamic changes in term of change in mean blood pressure. The sample size for this study was determined by the statistical formula $n=z^2$ PQ divided by d^2, where n is the sample size and z is the confidence coefficient, p is the rate of incidence of intraoperative hypertension in population and Q is 1-P and d is the error of estimation. By taking P as 30% and with a confidence of (z) 90% and with the error of estimate (d) of 10%, the minimum sample size worked out for this study as per the above formula is 80.

After obtaining approval of Hospital Ethical Committee along with written informed consent, patients aged between 25 and 75 years of American Society of Anesthesiology (ASA) physical status 1 or II, scheduled for elective laparoscopic colorectal surgery were enrolled in this prospective, double blind randomized placebo controlled clinical comparative study.

Exclusion criteria were patients with asymptomatic bradycardia (heart rate of less than 50 beat per min at rest), heart block greater than 1st degree, on beta blockers or alpha 2 agonist or history of allergy to alpha 2 adrenergic agonists, uncontrolled hypertension and pregnant patients or lactating mothers and those with history of drug/substance abuse. Emergency or re-exploration cases and patient not

able or unwilling to provide consent for the study were also excluded from the study.

Hundred patients were randomly allocated based on computer generated (www.randomizer.org) random sequence of numbers into two equal groups (50 in each)–Group D (dexmedetomedine) and Group P (placebo using normal saline). The randomization list was kept totally secret by the randomizer and the study personnel were totally unaware of the patient allocation and drug administration to each patient. Concealment of the study drug and group allocation was done strictly, drugs were loaded by only one anaesthetist (randomizer) who was not involve in the study and labeling of the drugs was done as numerical label according to the number of enrollment and all labeled as study drug @ 4 micrograms per ml be it a placebo or main study drug and the study personnel were totally unaware of the which drug being administered.

All patients were given Tab Alprazolam 0.5 mg orally the night before and on the morning of the surgery. On arrival in the operation theater, monitors were attached to record the baseline parameters heart rate, blood pressure and oxygen saturation.

After intravenous cannulation, patients were given glycopyrrolate 4 mcg/kg, midazolam 0.02 mg/kg, fentanyl 2 mcg/kg. Anaesthesia was induced with propofol 2 mg/kg, intubation was facilitated with atracurium 0.6 mg/kg. Anaesthesia was maintained with air, oxygen and sevoflurane. Muscle relaxation was provided by intermittent top up of atracurium as per the neuromuscular monitoring. Bi Spectral index (BIS) was used to adjust the sevolfurane concentration (2%-3%). Intraoperative analgesia was provided with continuous infusion of fentanyl at rate of 1 mcg/kg/hour. Controlled mechanical ventilation (volume controlled mode) and tidal volume (VT) of 8 ml per kg of predicted body weight, positive end expiratory pressure of 5 cm water and ventilator frequency was adjusted to maintain the $ETCO_2$ between 35 mmHg-45 mmHg.

After induction and establishment of mechanical ventilation, the study drug infusion was started as bolus of 1 mcg/kg over 10 min followed by an infusion at the rate of 0.2 mcg/kg/h which was continued postoperatively 12 hrs or total of 24 hours from the first initiation of infusion. All patients in group D as per the randomization chart had received dexmedetomidine and rest in group P received normal saline in similar rate.

Warming devices (fluid and air warmer) were used to maintain the temperature. Pneumo-peritoneum was created by insufflation of carbon-dioxide (CO_2) and intra-abdominal pressure was kept between 12 mmHg-15 mmHg throughout the surgical procedure. Intraoperative monitoring included continuous ECG, pulse rate, oxygen saturation, non-invasive blood pressures every 5 min and end-tidal CO_2, apart from BIS, nasopharyngeal temperature and neuromuscular monitor.

Mean arterial pressures (MAP) were maintained within +/- 30 % of the baseline values. In the presence of hypertension (defined as MAP values>30% of baseline values, on two successive readings) and/or tachycardia (defined as heart rate>30% of baseline values), additional fentanyl was given in doses of 0.5 mcg/kg, repeated if needed after 5 min till a maximum of 2 mcg/kg after which Labetalol infusion was reserved for refractory hypertension.

Hypotension (defined as MAP<30% of baseline values, on two successive readings) was treated with intravenous ephedrine 6 mg bolus along with fluid bolus of 200 ml lactated ringer solution and infusion of study medication was reduced to 50% of initial infusion rate. If hypotension persisted for more than 15 min, despite these measures study drug were stopped and the patient excluded from the study.

Bradycardia (defined as heart rate below 45/min and persisting for more than two min was treated with intravenous atropine 0.04 mg. If bradycardia persisted after atropine, the study drug was stopped and the patient excluded from the study. In case the patient required post-operative ventilation or intraoperative conversion to laparotomy, the patient were excluded from the study.

For laparoscopic surgery, dissection is made through four or five port sites and follows a medial to lateral approach after bowel mobilization, and an abdominal wall incision is made for extraction of the specimen. After retrieval and closure, pneumoperitoneum is created; hemostasis is achieved and is followed by port closure.

Sevoflurane and fentanyl infusion were stopped as soon as the laparoscopy ports were removed. At the end of surgery, after assessing the degree of block with a peripheral nerve stimulator neuromuscular blockade was reversed with 50 mcg/kg of neostigmine and 8 mcg/kg glycopyrrolate. Once the BIS value reached above 70 and patients were extubated once they regained sufficient muscle tone and start following verbal command. The time to eye opening, following verbal command and extubation after stoppage of sevoflurane were noted and recoded. After completion of the procedure, all patients were given intravenous paracetamol 1 gm, Tramadol 100 mg and ketorolac 30 mg which were repeated 8^{th} hourly in postoperative period.

Dexmedetomidine infusion at 0.2 mcg/kg/hr was continued into the post-operative period for another 12 h or till a total period of 24 h after initiation of infusion whichever is earlier. Post-operative pain was assessed every hour for first 3 h and then every 4 h using a 10 point verbal rating scale (VRS) with 0-no pain and 10-severe pain. Intravenous morphine 0.05 mg/kg was used as rescue medication when the VRS exceed more than 4 or the patient requests additional analgesia during the pain assessment. Postoperative nausea and vomiting was assessed and treated with ondanseteron 4 mg intravenously.

Data were collected using a standardized protocol, which includes demographic data, the total time of anesthesia (from induction to discontinuing of sevoflurane) and duration of surgery (from incision till the placement of surgical dressing). The additional doses of intra-operative fentanyl, need for labetalol, incidence of hypotension and bradycardia requiring interventions, time to eye opening and extubation, rescue analgesic requirements in postoperative period, incidence of postoperative nausea and vomiting and any requirement of anti-emetic were recorded for the first 24 h.

Data collected under the project were compiled, data are used as either percentage, mean ± Standard Deviation (SD) and analyzed statistically employing Z test for comparison of percentages between the two groups. The correlation between pulse, mean arterial blood pressure and analgesic requirement and pain scores was analyzed using Pearson Correlation coefficient. Analysis of Variance (ANOVA) was used to calculate the statistical difference between two groups under the study for the variables taken up for the study under different time intervals such as haemodynamic changes, analgesics requirement and VAS score. For direct comparison of means of the two groups Students independent t test was employed. All statistical analysis was performed with SPSS 23 (IBM Corporation). Data from excluded patients were not included for analysis.

Results

100 consecutive patients were selected and randomized into two groups with 50 in each group. Four patients from the Dexmedetomedine group (group D) and seven from the group P were excluded from the study. Reason for exclusion was conversion to laparotomy in 7 patients (3 in group D and 6 in group P) and 2 patients were electively ventilated overnight (one in each group).

The demographic profile, type and duration of surgeries and duration of anaesthesia in both the groups were similar as shown in Table 1.

Patient characteristics	Group D	Group P	P value
Age (years)	51.60 ± 15.86	48.68 ± 14.79	P=0.95
Males/Females	27/19	23/20	P=1.28
Weight (kg)	60.36 ± 5.86	59.781 ± 5.44	P=0.98
Mean duration of anaesthesia (h)	5.558 ± 2.340	4.734 ± 1.614	P=1.06
Mean duration of surgery (h)	5.118 ± 2.190	4.82 ± 1.529	P=0.978
ASA I/II	33/13	29/14	P=1.79

Table 1: Demographic data of the two groups.

Baseline haemodynamic parameters were comparable in both the group, difference in the haemodynamic parameters (MAP and Heart rate) started after about 15 min after intubation that reached statistically significance after 30 min, the difference persisted despite the use of labetalol in few patients in control group, and the difference slowly faded in postoperative period over next 6-8 h (Figure 1). Five patients in the control group required labetalol infusion at some point of surgery which was slowly tapper off in postoperative period. There was statistically significant difference between the two groups in terms of intraoperative requirement of fentanyl (Table 2). Nine patients in the control group and thirty four patients in the study group did not require additional dose of fentanyl. The mean eye opening time, time to obey command and time to extubation after turning off sevoflurane was comparable in both the groups (Table 3).

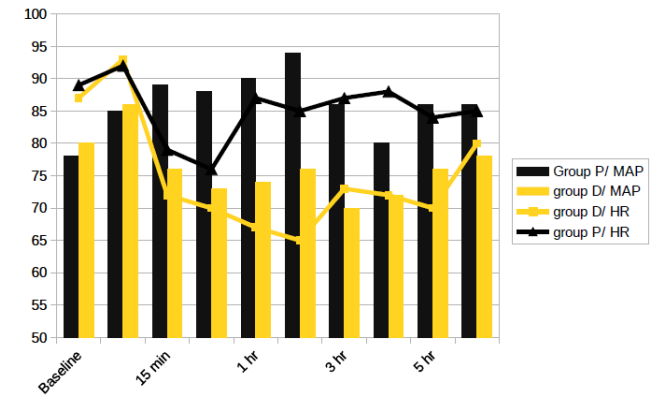

Figure 1: Intraoperative MAP and HR in both the groups.

Fentanyl doses	Group D	Group P	P value
No fentanyl	34	9	P=0.0015
0.5 mcg/kg	8	7	P=2.05
1 mcg/kg	2	10	P=0.008
1.5 mcg/kg	2	4	P=0.02
2 mcg/kg	0	13	P=0.0007

Table 2: Requirement of additional intraoperative fentanyl between the two groups.

Few patients in group P had cardiovascular side effects in the form of intraoperative cardiac arrhythmia (ventricular ectopic, atrial fibrillation and supra-ventricular tachycardia) in three patients and one patient had shoot in blood pressure following extubation requiring labetalol infusion. Five patients had intraoperative hypotension in the dexmedetomidine group. They were treated with intravenous fluid and ephedrine 6 mg boluses. Two patients recovered with this and the others required a reduction in the dexmedetomedine to half for half an hour. Two patients in the study group had bradycardia which responded to a single dose of atropine 0.4 mg. Among these complications only hypotension was found to be significant between the two groups. However, these complications were not clinically significant.

Variables	Group D	Group P	p value
Mean time to eye opening (min)	14.72 ± 2.04	14.67 ± 1.56	P=0.95
Mean time to extubate (min)	15.59 ± 8.25	15.37 ± 6.25	P=1.15
Mean time to obeying commands	17 ± 9.21	16.64 ± 8.82	p=1.02

Table 3: Comparison of mean time to eye opening, extubation and obeying commands.

Postoperative time 0 is the time immediately after extubation and fifteen patients in group D and eleven patients in group P did not require additional analgesic at time 0, rest of the patients in each group required additional rescue analgesics. There was no statistical difference in the doses of morphine between the two groups (Table 4). Only three patients in group D required a single dose of anti-emetic and one patient in both study and control group required two doses of anti-emetic. There was no statistical difference in the requirement of anti-emetic between the two groups (Table 5).

No of dose	Group P	Group D	Z value	P value
No dose	25.58%	32.61%	0.73	p=0.75
One dose	34.88%	43.38%	0.83	p=9.02
Two doses	27.81%	23.54%	0.48	p=1.21
Three doses	11.63%	2.17%	0.82	p=2.34

Table 4: Percentage of patients requiring number of rescue analgesic (morphine) in postoperative period.

No of dose	Group P	Group D	Z value	P value
No dose	97.67	91.30	1.30	p=1.3
Single dose	0.00	6.52	1.70	P=2.0
Two doses	2.33	2.17	0.05	p=0.95

Table 5: percentage of patients in each group requiring postoperative antiemetic (Ondansetron).

Discussion

Unlike laparotomies, laparoscopic colorectal surgeries are of longer duration, technically more difficult, greater physiologic alteration with intra-operative changes in position, intermittent inflation and deflation of pneumoperitoneum [1,2,7]. Creation of Pneumo-peritoneum affects physiology of several homeostatic mechanisms and acid-base balance due to absorption of insufflated carbon-Dioxide. The cardiovascular changes due to pneumo-peritoneum include increase in mean arterial pressure, decrease in cardiac output and an increase in systemic vascular resistance which produces significant hemodynamic changes, especially in elderly and in hemo-dynamically compromised patients may often compromise tissue perfusion [8]. Several techniques have been proposed to provide haemodynamic stability during laparoscopy. These include nitroglycerine, labetalol, clonidine and dexmedetomidine [4,5,7,9]. We used the manufacturer recommended dosing of 1 mcg/kg bolus of dexmedetomidine followed by 0.2 mcg/kg /hr as infusion which was the lowest recommended dose for infusion to find its usefulness in maintaining intraoperative and postoperative haemodynamic stability in laparoscopic colorectal surgeries [3]. We found that even the lowest recommended dose of dexmedetomedine produced significant haemodynamic stability during laparoscopic colorectal surgery without significantly delaying the recovery from anaesthesia even with prolonged use.

Difference in the haemodynamic parameters (MAP and Heart rate) started about 15 min after intubation that reached statistically significance after 30 min, the difference persisted despite the use of labetalol in few patients in control group, and the difference slowly faded in postoperative period over next 6-8 h. The difference in MAP and HR despite labetalol infusion might be explained by the fact that dexmedetomidine group had lower mean MAP and HR compared to higher mean value in the control group. Labetalol was used in 5 patients in control group, but only when the MAP was greater than 30% of baseline value, none of the patient in study group required labetalol.

Tanskanen et al. in their study showed that intra-operative infusion of dexmedetomidine at a rate of 0.4 μg/kg/h maintains heart rate and blood pressure in acceptable range for a longer duration as compared to placebo group [10]. We did find a statistically significant difference in fentanyl requirement during the intra-operative period. Although the requirement of additional fentanyl within first 15 min to 30 min after pneumoperitoneum was similar in both the groups. Dexmedetomedine is known to have analgesic, amnesic and sedative properties. These can subsequently reduce the dose of intra-operative opioid and anaesthetic requirement. Dexmedetomedine decreases sympathetic tone and haemodynamic responses to surgical stimuli and pneumoperitoneum. Its hemodynamic effects are due to central sympatholytic and peripheral vasoconstrictive effects [3,10]. This reduction in stress response is found to be cardio protective. So this is found to be beneficial in elderly patients with cardiovascular diseases. We also found that use of dexmedetomedine significantly reduces the use of labetalol for control of hypertension and tachycardia associated with the creation of pneumoperitoneum. We have found that hypotension was a complication that occurred significantly higher in the study group. Both bradycardia and hypotension can occur with dexmedetomidine, but both are often self-limiting and can be easily treated. Bradycardia is one of the most significant side effects associated with dexmedetomedine with higher doses but with a dose of 0.2 mcg/kg bradycardia was not a significant side effect [6].

Most clinical studies showed a decrease in postoperative PCA morphine consumption without a reduction in pain scores which may be attributed to the analgesic effect by dexmedetomidine. In contrast to those reports, however, we did not find a significant reduction in postoperative opioid consumption in patients who received dexmedetomidine. The opioid sparing effect of dexmedetomidine is dose related. It was estimated that a dose of 0.5 mcg/kg/h dexmedetomidine had the maximum postoperative analgesic and opioid sparing effects [8,11]. Activation of opioid receptors is believed to provide better pain control in comparison to alpha 2 receptors. Dexmedetomidine is more of a sedative than analgesic at low dosage [12-14].

We used a minimal recommended dose of dexmedetomidine infusion which might be the probable reason we could not get the significant opioid sparing effect in the postoperative period. To date, only a few studies have explored postoperative recovery after the use of intra-operative dexmedetomidine. Emergence agitation is less and stability of recovery is better when dexmedetomidine is used [12,15]. Delayed recovery due to the sedative properties of dexmedetomidine has been reported in several studies [16-18]. We did not have any significant delay in extubation, eye opening or following commands following extubation. This was even when we did not stop the infusion even after the surgery. Most sedatives other than dexmedetomidine have to be discontinued during extubation [19].

Laparoscopic surgeries are associated with increased incidence of nausea and vomiting due to multifactorial issues, we did not find a significant difference in the anti-emetic requirement between the two groups. Only four patients in the study group and one patient in the control group required anti-emetics. The anti-emetic effect of intravenous dexmedetomidine was seen when doses of 0.5 mcg/kg/h-1 mcg/kg/h was used. This effect may be due to direct anti-emetic properties of α_2 agonists, a decrease of sympathetic tone and a reduction in intra-operative opioid use [20].

Conclusion

Low dose Dexmedetomidine infusion as an adjunct to general anaesthesia appears to be a provide significant hemodynamic stability in laparoscopic colorectal surgery. However, it has limited analgesic and antiemetic effects. Further studies are needed to define the optimum dose response relationship of dexmedetomidine.

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