Original Article

A randomised controlled trial to evaluate the peri-operative role of intraoperative dexmedetomidine infusion in robotic-assisted laparoscopic oncosurgeries

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ABSTRACT

Background: Robotic and minimal invasive surgeries pose challenges to the anaesthesiologists. Dexmedetomidine (dexmed), with distinct properties of sedation and analgesia has emerged as a promising drug. Our primary aim, in this double-blinded study, was to evaluate reduction in the intraoperative opioid requirement with the use of intravenous dexmed infusion. Secondary objectives included effect on intraoperative anaesthetic and postoperative analgesic requirement. **Methodology:** After approval from Ethics board and registration of the trial, 46 eligible patients planned for robotic oncosurgeries (abdomen) were included. As per computer generated randomisation chart, patients were randomised into either dexmed or saline group. Five minutes after insufflation of the abdomen, the study drug bolus—saline or dexmed (1 μg/kg) was given over 10 min and was followed by maintenance infusion (0.2 μg/kg/h) until release of pneumoperitoneum. Study drug titration, fentanyl boluses, and changes in minimum alveolar concentration (MAC) of inhalational agent were protocolised. **Results:** The mean intraoperative fentanyl requirement was significantly lower in the dexmed group 192.6 μg (±66.4) versus the saline group 260.7 μg (±88.6), $P = 0.013$. The MAC requirement of inhalational agent was significantly lower in the dexmed group. Intraoperative episodes of hypotension and bradycardia were similar in both groups. First analgesic request, 24 h postoperative pain scores and side effects profile were comparable in both groups. **Conclusion:** Intraoperative dexmed (bolus of 1 μg/kg followed by 0.2 μg/kg/h infusion) has an opioid and inhalational anaesthetic sparing role during robotic oncosurgeries. However, no benefit of the infusion is seen in the postoperative period.

Key words: Dexmedetomidine, peri-operative care, pneumoperitoneum, robotic surgical procedures

INTRODUCTION

Robotic surgeries have revolutionised surgical outcomes. They offer the benefits of laparoscopic surgery such as improved cosmetics, reduced postoperative pain, wound complication, and faster recovery with shorter hospital stay.[1] Robotic surgery also overcomes some of the shortcomings of conservative laparoscopic or endoscopic techniques. It presents three-dimensional views with magnification; and tools with seven degrees of freedom that are capable of duplicating hand movements with high accuracy.[1,2]

Robotic surgery poses challenges to the anaesthesiologists with respect to perioperative management. Pneumoperitoneum and carbon dioxide

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insufflation leads to increase in plasma catecholamine levels and plasma renin activity.[3] Agents currently used to blunt the sympathetic discharge and provide haemodynamic stability include opioid analgesics, benzodiazepines, beta blockers, calcium channel blockers, and vasodilators.[4] In recent times, dexmedetomidine (dexmed) has emerged as a promising drug. It is a highly selective α2 adrenergic receptor agonist which possesses the properties of sedation and analgesia.[4,5] We planned to study the use of dexmed in robotic surgeries and evaluate its effects on intraoperative haemodynamics, anaesthetic, intraoperative opioid requirement, and need for rescue analgesics in the immediate postoperative period.

METHODS

This prospective double-blinded randomised controlled trial was conducted in our hospital from September 2015 till November 2016. After the Institutional Ethics Committee approval (dated- 4/08/2015), CTRI registration [CTRI/2015/08/006130] and written informed consent, 46 adult patients with American Society of Anesthesiologists (ASA) Physical Status class I and II, undergoing robotic oncosurgeries (abdomen) were included. Contraindications to the use of dexmed like severe liver and renal dysfunction, patients with heart block or bradycardia, premature ventricular ectopics >5/min and, in addition, hypertensives were excluded from the study.[6] Patients in whom a mini laparotomy (more than 5 cm) was planned either for tumor delivery or anastomosis were not included.

Based on the monthly audit data report of 12 adult patients who underwent similar robotic oncosurgeries at our center, it was found that the mean intraoperative consumption of fentanyl was 355 μg (±111 μg). Considering a 30% reduction of fentanyl as meaningful, a group sample size of 19 each was achieved at 82% power with a significance level (alpha) of 0.05 using a two sided Independent *t*-test. To account for intra/postoperative exclusions (conversion to open laparotomy, inoperability due to advanced disease, need for postoperative ventilation), the sample size was taken as 23 in each arm with a total of 46 patients.

Preoperatively, the patients were briefed about the trial and explained about the use of pain scales. Blood pressure, plethysmography, and continuous electrocardiography were monitored for all patients in the operating room. Anaesthesia induction was standardised as follows. After preoxygenation with 100% oxygen for 3 min using a closed circuit with 6–8 L flow, general anaesthesia was administered. Injection fentanyl (2 μg/kg) and propofol 2–3 mg/kg, was given intravenously in incremental doses until absence of response to verbal command. Rocuronium bromide 1 mg/kg was used to facilitate intubation. Airway was secured using suitable sized endotracheal tube. Intraoperative anaesthesia was maintained using air–oxygen mixture to achieve a fractional concentration of oxygen between 0.4 and 0.5. Isoflurane/sevoflurane was used to obtain a minimum alveolar concentration (MAC) of 0.7–1.2 Repeat doses of relaxants were administered when the train of four (TOF) count was 2 or more. Ventilation parameters were adjusted to maintain end-tidal carbon dioxide (CO2) of 40 +/-5 mm Hg.

The patients were divided into two groups-saline group and dexmed group. The randomisation was as per computer generated sheets and allocation concealment was maintained using brown sealed envelopes containing the study drug for the unblinded team. The unblinded team prepared the study drug and handed it over to the operating room team. The study drug was started 5 min following pneumoperitoneum, a bolus followed by maintenance infusion as advised by the unblinded team. The dexmed group received 1 μg/kg bolus for 10 min followed by maintenance of 0.2 μg/kg/h. The saline group received equivalent dose of normal saline. Intraoperative titration of study drug with respect to haemodynamic parameters was as per protocol [Figure 1]. For the study, bradycardia was defined as heart rate less than 45 beats/min and hypotension was defined as mean arterial pressure (MAP) less than 60 mm of Hg.

The study drug infusion was stopped at the release of pneumoperitoneum. Isoflurane/Sevoflurane was discontinued after skin closure and in conjunction with the extent of neuromuscular blockade. Injection bupivacaine 0.25% was used for infiltration of port entry sites, 3–5 ml at each port site to ensure maximum permissible volume was not exceeded in any patient. All patients received injection metoclopramide 10 mg and injection paracetamol at 15 mg/kg (less than 50 kg body weight) or 1 gm (body weight more than 50 Kg) at the end of surgery for postoperative analgesia. Neostigmine 0.05 mg/kg and glycopyrrolate 8 μg/kg intravenously were administered for reversal of neuromuscular blockade after confirming a train of four count of 2 or more.

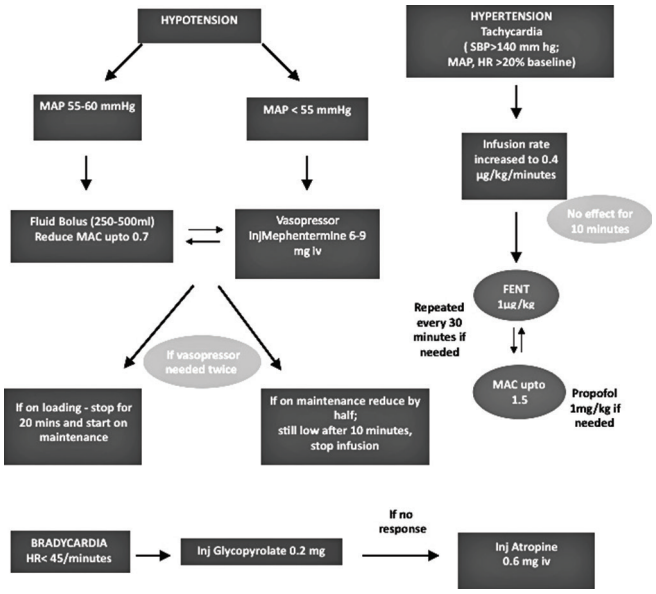

Figure 1: Flowchart for titration of study drug and anaesthetic drugs in response to patients' haemodynamic parameters (SBP- systolic blood pressure, MAP – mean arterial pressure, HR – heart rate, MAC – minimum alveolar concentration of inhalational agent)

In the recovery room and till 24 h postoperatively pain scores were assessed using numerical pain rating scale (1–10, 10-worst pain) at rest and movement. If patient complained of pain more than 3/10 at rest or more than 4/10 at movement, injection fentanyl 0.5 µg/kg was given intravenously as rescue analgesic and the time of demand was noted. Following the first rescue analgesic, diclofenac 1 mg/kg (max 75 mg) or paracetamol 15–20 mg/kg was prescribed round the clock with tramadol 50 mg IV on need basis (max 50 mg three times a day). Pain scores were recorded at 30 min, 1, and 2 h post-surgery and every 6 h. The average of all readings at the end of 24 h was compared. Sedation scores using Ramsay sedation score (RSS) and number of episodes of nausea and vomiting in the immediate postoperative period (till 2 h) were noted.

Demographic details such as age, gender, body weight, type of surgery, duration of anesthesia and surgery (hours), positioning of patient were recorded. Time of inflation and release of pneumoperitoneum, intra-abdominal pressures were noted. Pre-induction haemodynamics (baseline values-T0) and intraoperative haemodynamics such as blood pressure (BP), [systolic, diastolic and MAP] and heart rate (HR) were monitored at start of the pneumoperitoneum, and at 5 (start of study drug), 10, 20, and every 30 min until the release of pneumoperitoneum (the end of study drug infusion). Any episodes of bradycardia, hypotension, MAC value of inhalational agent and intraoperative fentanyl consumption was noted. Recovery time, defined as time for eye opening after inspiratory inhalational agent value becomes zero on the gas monitor, was assessed.

Demographic data were expressed as mean ± standard deviation (age, weight, height, duration of surgery, anaesthesia) or proportion (sex and ASA physical status). Numerical parameters were analysed using Student's independent *t*-test when normally distributed (fentanyl use, time to eye opening, rescue analgesic request, to ambulate) and with Mann–Whitney U-test, if otherwise (HR, BP, MAC and pain scores). All the raw data were entered and analysed using Statistical Package for Social Sciences (SPSS) (IBM, NY, USA) statistical software version 25. All the analyses were two tailed, and confidence level was 95%. $P < 0.05$ was considered statistically significant.

RESULTS

Fifty-one patients were found eligible, 46 patients were randomised, and data from 40 patients were included in the final analysis, refer to consort diagram- Figure 2. The general demographics such as age, gender, weight, ASA physical status, surgical details were comparable between the two groups [Table 1].

The mean of total intraoperative fentanyl used was significantly lower in the dexmed group; 192.6 µg (±66.4) versus 260.7 µg (±88.6) in saline group, $P = 0.013$. Intraoperative vital parameters were similar in both groups [Figure 3]. There was no difference in adverse events including bradycardia and hypotension [Table 2]. Three patients in the dexmed group needed increase in the maintenance infusion rates to 0.4 µg/kg/h in response to hypertension and 5 patients in the Dexmed group required a decrease on the maintenance infusion rates from 0.2 µg/kg/hr to 0.1 µg/kg/h in response to hypotension. There was no instance of discontinuation of study drug infusion due to hypotension or bradycardia in the dexmed group. The MAC requirement of inhalational agent was significantly lower in the dexmed group at 30 min ($P = 0.02$), 1 h ($P = 0.017$), and 2 h ($P = 0.028$) [Figure 3].

In the postoperative period, the first analgesic request was earlier in the saline group but was not statistically significant ($P = 0.78$) [Table 2]. There was no difference in recovery time and time to ambulate postoperatively in both the groups. The pain scores were comparable between the two groups [Figure 4].

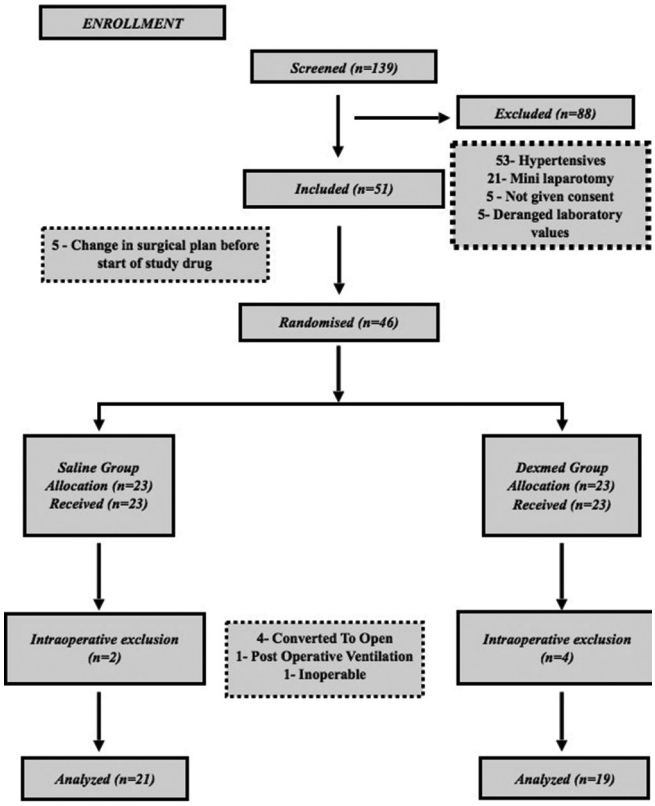

Figure 2: Consort flow chart for patient recruitment into the trial. Dexmed – dexmedetomidine

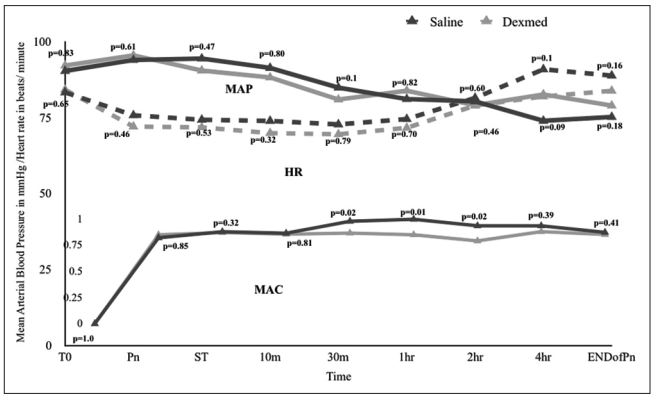

Figure 3: Comparison of intraoperative haemodynamic parameters and anaesthetic drug requirement between two groups (MAP – mean arterial pressure, HR – heart rate, MAC – minimum alveolar concentration of inhalational agent, Dexmed – dexmedetomidine) T0- pre induction, Pn- At creation of pneumoperitoneum, ST – start of study drug (5 min after creation of pneumoperitoneum), ENDofPn- End of pneumoperitoneum (stoppage of study drug) $P < 0.05$ is significant

The incidence of postoperative nausea at the end of 2 h was 8.7% (2 patients) in both the groups ($P = 0.15$) while vomiting was 4.3% (1 patient) in the saline group and 8.7% (2 patients) in the dexmed group ($P = 0.3$). The RSS scores did not show significant difference between the two groups at multiple points of time.

DISCUSSION

The results of the study prove that intraoperative dexmed infusion after a loading dose of 1 μg/kg with maintenance of 0.2 μg/kg/h in robotic oncosurgeries has significant intraoperative fentanyl sparing effect. However, at the above dose, no benefit was seen in the postoperative period. There was no difference in pain scores, time to first rescue analgesic request, time to ambulate and postoperative side effects such as sedation, nausea, and vomiting observed between the groups in the first 24 h postoperatively.

Robotic-assisted laparoscopic surgeries have specific anaesthesia requirement.[7,8] During initiation of pneumoperitoneum, severe bradycardia and asystole has been noted in literature, hence the study drug was started 5 min after creation of pneumo-peritoneum to avoid compounded cardiac events during insufflation of the abdomen.[9,10] The use of dexmed has been studied extensively in laparoscopic surgeries;[11-13] however there is limited but growing data with the use of dexmed in robotic surgeries.[14,15] Though one may argue that the principles of laparoscopic surgery can be extrapolated to robotic surgery, one must understand that there remains a difference in the two surgical approaches**.** Literature has shown in addition to the need of steeper positions,[16] robotic surgeries have prolonged duration and more opioid use when compared to their laparoscopic counterparts.**[17]** Knowing the drawbacks of opioids such as delayed recovery, postoperative nausea, vomiting, urinary retention, it becomes more essential to study opioid sparing strategies in this surgical group.[18]

Three different infusion rates of dexmed (0.2 μg/kg, 0.4 μg/kg vs. 0.8 μg/kg per hour) were used in a previous trial and the impact of the same on intraoperative opioid requirement was compared in laparoscopic bariatric surgeries.[13] No significant difference in the opioid usage was seen among the different dexmed rates. Also there was no change in morphine consumption when compared to control in the postoperative period. Interestingly, this study showed a high requirement of vasopressor rescue (50%) in the dexmed 0.8 μg/kg and 15% discontinuation of study drug infusion in both dexmed 0.4 μg/kg and dexmed 0.8 μg/kg groups. To minimise the use of vasopressors intraoperatively, we selected a lower rate for the maintenance infusion with provision to increase the same if needed. In our study, the intraoperative haemodynamic changes remained comparable between the study group and saline group.

Table 1: General demographics between the two groups

Parameters	Saline group *n*=21	Dexmed group *n*=19	*P*
Age in years: mean (±SD)	47.2 (±13)	51.8 (±12)	0.1
Sex			
Male	7	7	
Female	14	12	0.8
Weight in kg: mean (±SD)	57.3 (±10)	65.2 (±13)	0.08
ASA physical status			
ASA I	15	9	
ASA II	6	10	0.12
Nature of surgery			
Hysterectomy	11	6	
Prostatectomy	3	3	0.9
Cholecystectomy	0	3	
Anterior resection	3	1	
Pancreatectomy	0	2	
Nephrectomy	3	4	
Liver metastectomy	1	0	
Position during surgery			
Trendelenberg	17	10	0.08
Reverse tredenlenberg	1	5	
Left lateral	3	4	
Duration of SX (min)	337.6±95	341.2±91	0.8
Duration of pneumoperitoneum (min)	269.2±95	271.2±101	0.9

Dexmed - dexmedetomidine, SX=surgery, SD=Standard deviation

Table 2: Intra-operative haemodynamic events and post-operative parameters between the two groups

Parameters expressed as no of patients (%)	Saline group *n*=21	Dexmed group *n*=19	*P*
Intraoperative bradycardia	2 (9.5%)	6 (31.6%)	0.08
Vagolytic use	2 (9.5%)	5 (26.7%)	0.39
Intraoperative hypotension	6 (28.6%)	7 (36.8%)	0.577
Mephentermine use	5 (22.7%)	7 (36.8%)	0.26
Infusion rate increased	8 (36.4%)	5 (26.7%)	0.43
Infusion rate decreased	2 (9.5%)	6 (31.6%)	0.08
Time to eye opening (min)	15.7 (±2)	15.2 (±1)	0.17
Time for rescue analgesia (min)	97.9 (±61)	117.9 (±121)	0.78
Time to ambulate (hours)	19.6 (±5)	18.7 (±6)	0.69

Dexmed - dexmedetomidine, *P*<0.05 considered significant

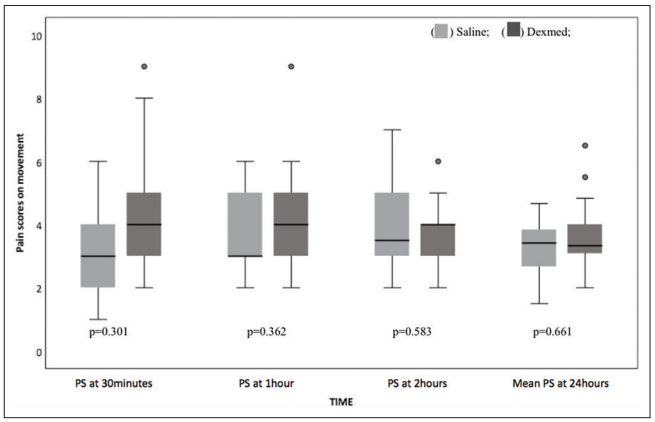

Figure 4: Box plot comparing pain scores at movement between the two groups in the post –operative period. PS- pain scores, Dexmed – dexmedetomidine

In our study we found opioid sparing effect with the use of dexmed in the intraoperative period. One can challenge the clinical benefit of the difference in 60–70 μg of fentanyl seen between the two groups. It is important to evaluate the inhalational anaesthetic sparing effect at the same time. When we compared the MAC requirement of inhalational agents between the two groups, we found a significant reduction in use of anaesthetic agents in the dexmed group in comparison to saline group. This could have resulted in lower fentanyl consumption in saline group- 260.7 μg (±88.6) as seen in comparison with our audit findings -355 μg (±111 μg). Previous laparoscopic studies have also found similar anaesthetic sparing effect with use of dexmed.[19,20]

Similar to other studies, we did not find significant difference in recovery time comparison between the two groups.[13,14] Benefit of intraoperative dexmed infusion for postoperative pain is debatable, with a few studies showing a benefit[5,20] while others not showing any advantage.[13] Our study failed to show any difference in the time for rescue analgesic and thus significant analgesic benefit. This could be attributed to the extensive tissue dissection and longer duration of surgery commonly seen with respect to oncosurgeries. As noted in a previous study the postoperative side effects such as sedation, nausea, and vomiting were similar in both groups.[21]

The study is not without limitations. Patients with hypertension were not included in the trial to simplify the study drug titration to MAP of 60 mm of Hg in all cases. However, this does not imply that the drug cannot be used in hypertensives, we suggest that use of dexmed in these patients be individualised and titrated to higher MAP. Secondly, we did not look at hard end outcomes such as length of hospital stay and time of discharge due to variations in individual unit protocols. With the trending of enhanced recovery protocols much emphasis is on minimising intraoperative opioid usage; dexmed can play a promising role and must be incorporated in suitable multi-modal anesthetic plan in robotic oncosurgeries.

CONCLUSION

Dexmed at dose 1 μg/kg followed by maintenance of 0.2 μg/kg/h has significant intraoperative fentanyl and inhalational anaesthetic sparing effect without causing haemodynamic instability. However, no benefit of the infusion was seen in the postoperative recovery and pain scores.

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Conflicts of interest

There are no conflicts of interest.

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