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EFFECT OF CONTINUOUS INFUSION OF DEXMEDETOMIDINE AND ESMOLOL ON HEMODYNAMIC ATTENUATION AND POST-OPERATIVE OPIOID REQUIREMENT IN PATIENTS UNDERGOING LAPAROSCOPIC DONOR NEPHRECTOMY. A RANDOMIZED PARALLEL GROUP TRIAL.

Anaesthesiology

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ABSTRACT

Background: Laparoscopic surgeries are associated with haemodynamic responses due to pneumoperitoneum. Both dexmedetomidine and esmolol have been used for attenuating these responces in laparoscopic cholecystectomy.
Aims: This double blinded randomized parallel group trial was planned to compare intraoperative hemodynamics and postoperative opioids requirement in patients undergoing laparoscopic donor nephrectomy.
Methods: All patients underwent surgery under general anaesthesia. 50 patients in Group D received 1µg/kg dexmedetomidine over 15-minutes, then at 0.5µg/kg/hr. 49 patients in Group E received 1mg/kg esmolol over 15-minutes then at 15µg/kg/min.
Results: Adequate attenuation of heart rate and blood pressures occurred in response to pneumoperitoneum in both the groups. Haemodynamic responses and postoperative fentanyl required in 24-hours were significantly low in patients receiving dexmedetomidine.
Conclusion: Dexmedetomidine effectively lowered postoperative opioid requirement in comparison to esmolol. The hemodynamic response to pneumoperitoneum was adequately suppressed in both the groups.

KEYWORDS

Dexmedetomidine, Esmolol, Laparoscopic donor nephrectomy.

INTRODUCTION

Laparoscopic surgeries are associated with adverse hemodynamic changes like increased systemic vascular resistance (SVR), hypertension and tachycardia, forcing the anesthesiologist to increase the depth of anaesthesia or incorporate an array of drugs including vasodilators to maintain haemodynamic response.[1] Various drugs like propofol, opioids, magnesium, dexmedetomidine and esmolol have been tried with varying success rate.[2-5]

Dexmedetomidine is α-2 adrenergic agonist with sedative, analgesic and anxiolytic properties. Various studies have demonstrated that it decreases opioid requirements and attenuates hemodynamic response in laparoscopic surgeries.[5-6] Esmolol is ultra-short acting ß adrenergic antagonist which has been used during laparoscopic surgeries to decrease perioperative hemodynamic changes.[5] Moreover, esmolol, which do not possess analgesic properties *per se*, has shown to reduce intra-operative and postoperative opioid consumption.[7]

Several studies have shown the effects of two drugs to attenuate stress response after creating pneumoperitoneum for laparoscopic surgeries with either mixed results[5,8] or equal efficacy.[9] However most of the studies have been conducted in laparoscopic cholecystectomy. We wished to see if the results could be mimicked for urological surgeries as well. So, this double-blinded parallel group study was designed to compare the effects of dexmedetomidine and esmolol on intraoperative hemodynamics and postoperative opioid requirement in laparoscopic donor nephrectomy. It also aimed to compare their effect on postoperative nausea and vomiting (PONV) and other side effects.

MATERIALS AND METHODS

The present study was conducted from December 2013 to April 2014 after Institutional Ethics Committee approval and registering the trial in Clinical trial registry of India (CTRI/2014/01/004268). Written informed consent was taken from all patients.

Hundred ten American Society of Anesthesiologists (ASA) physical status I and II patients aged 19-60 years undergoing laparoscopic donor nephrectomy were assessed for eligibility. Patients who didn't gave consent, patients on chronic use of opioids or ß adrenergic receptor antagonists, known asthma or reactive airway disease or allergic to any of two drugs were excluded.

Patients enrolled were randomized by computer generated random numbers and sealed envelope technique into two groups, to receive either dexmedetomidine (Group D) or esmolol (Group E). Group D received loading with 1µg/kg dexmedetomidine intravenous (i.v) over 15-minutes and then infusion of 0.5µg/kg/hr. Group E received loading with1mg/kg esmolol i.v over 15-minutes, then infusion of 15µg/kg/min. The study drugs were prepared by an anaesthesiologist not involved in the study. Loading drugs were prepared in similar 20-ml syringes and labelled "Loading". For maintenance infusion, a separate 20-ml preparation of drug was used in concentration of 5.5µg/ml of dexmedetomidine and 10mg/ml of esmolol and labelled in both the groups. For maintenance 0.9xbody-weight/10 was given as ml/h. The anaesthesiologist in operating room (OR), unaware of the contents of 20-ml syringes, collected data both in OR and post-operative care unit (PACU).

All the patients underwent transperitoneal laparoscopic nephrectomy under general anesthesia (GA) with endotracheal intubation. The "loading" drug followed by "maintenance" was initiated after lateral kidney position was made, post induction of GA. The drug was stopped after completion of surgery and before turning the patient supine. 2µ/kg i.v fentanyl was given at induction of anesthesia followed by 1µg/kg hourly boluses. 1gm paracetamol i.v was given prior to carbon dioxide (CO2) insufflation and then continued eight hourly in postoperative period. All patients were infiltrated with 0.5% ropivacaine at port sites and kidney retrieval wound after completion of surgery. Patients were also given i.v patient controlled analgesia (PCA) pumps with 10µg/ml fentanyl. 25µg boluses were delivered by PCA per dose, lockout interval of 5minutes with maximum four doses per hour without any background infusion was set.

Primary outcomes were hemodynamic parameters recorded at baseline, on starting and completion of study drug, CO2 insufflation, at CO2 de-sufflation, at extubation and after shifting to PACU and total fentanyl consumed over 24 hours. Secondary outcomes were number of patients having bradycardia (HR<45/minute), hypotension or hypertension (Mean arterial pressures MAP <30% or >30% of baseline) at any point under anesthesia and number of patients having PONV over 24 hours.

SAMPLE SIZE CALCULATION:

The variable total fentanyl consumed postoperatively over 24hours

was used for sample size calculation. Considering significance level α=0.05 and power of the test as 0.9(90%), a standard deviation of 75 µg, in 24 hours postoperative fentanyl requirement and critical difference between two groups taken as 50µg, the number of cases per group were 47 patients. We included 100 patients. https:// clincalc. com/Stats/SampleSize.aspx was used for sample size calculation.

RESULTS

The consort diagram shows the requirement, intervention and analysis journey of patients in this study (Figure1).

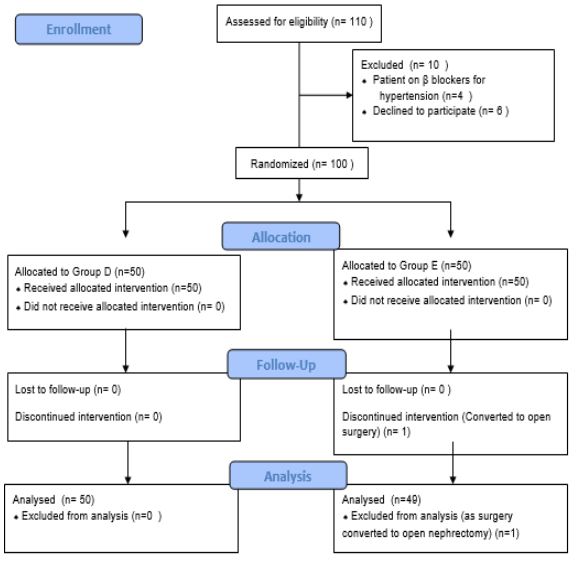


Figure 1: Consort diagram

The demographics, duration of anaesthesia and intraoperative fentanyl requirement were similar in both the groups.

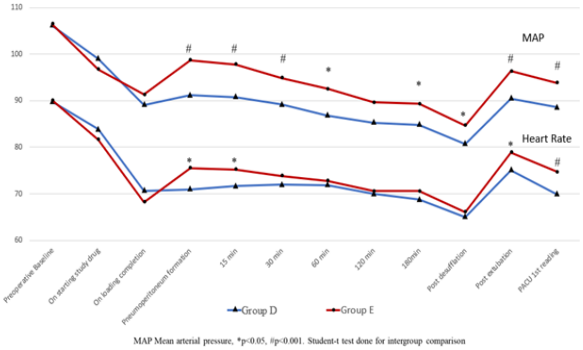
Table 1: Patient Demographics and other Comparable Data

	Group D (N=50)	Group E (N=49)	P values
Age (Yrs)*	43.24± 8.26	44.12 ± 6.99	0.568
Weight (Kg)*	64.92 ± 9.61	66.08 ± 11.82	0.593
Height (m)*	152±15	157± 10	0.054
M:F ratio#	6/44	2/47	0.281
ASA status (1/2)#	45/5	42/7	0.729
Duration of Anaesthesia (hours)*	4.69±0.52	4.65±0.56	0.713
Intoperative Fentanyl used (µg)*	389.6±51.89	382.55±51.34	0.498

*Student-t test done. #chi-square test done.

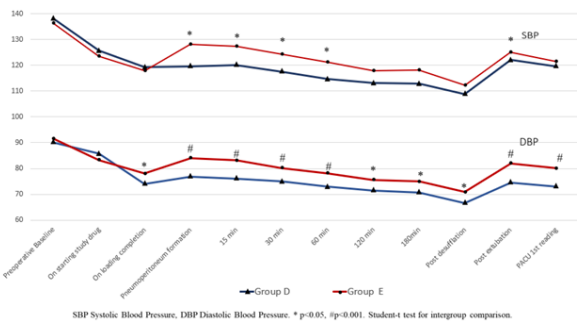
The hemodynamic parameters like heart rate (HR), Mean arterial pressure (MAP), Systolic (SBP) and diastolic blood pressure (DBP) were significantly lower in group D at pneumoperitoneum formation, at 15-minutes, extubation and in PACU. In addition, MAP and DBP were significantly lower throughout the surgery after pneumoperitoneum.

FIGURE 1: Trend of Haemodynamics. Heart Rate and MAP



MAP Mean arterial pressure, *p<0.05, #p<0.001. Student-t test done for intergroup comparison

FIGURE 2: Trend of Haemodynamics. Systolic and Diastolic Blood Pressures.



SBP Systolic Blood Pressure, DBP Diastolic Blood Pressure. * p<0.05, #p<0.001. Student-t test for intergroup comparison.

Group D had significantly lower post-operative fentanyl consumption in 24hours.

Table 2: Post-Operative Fentanyl Requirement.

	Group D (N=50)	Group E (N=49)	P value
24hours Fentanyl requirement (µg) (Mean±SD)	342.5 ± 88.67	449.48 ± 107.95	<0.001

The incidence of side effects in the groups over 24hours post-surgery is depicted in Table 3.

Table 3: Side Effects in 24-hours postoperatively.

	Group D (N=50)	Group E (N=49)	p value
Bradycardia	8	5	P=0.393
Hypotension	14	9	P=0.256
Hypertension	0	2	--
PONV	8	3	P= 0.117

PONV: Postoperative nausea and vomiting. Data presented as number of patients. Chi-Square test done.

DISCUSSION

The present study shows that both dexmedetomidine and esmolol successfully controlled hemodynamic changes during pneumoperitoneum in laparoscopic surgeries; however, dexmeditomidine attenuated these responses to a greater extent than esmolol. In addition, it also decreased postoperative opioid requirement.

Pneumoperitoneum during laparoscopic surgery leads to significant hemodynamic changes such as increase in HR, MAP and SVR and a decrease in cardiac output. The decline in cardiac output can be attenuated by volume infusion before pneumoperitoneum. However, an increase in MAP and SVR requires therapeutic interventions like β-blockers, opioids, nitroglycerine, and α-2 adrenergic agonist.

In our study we observed that HR and MAP were significantly lower in dexmedetomidine group as compared to esmolol at time points like pneumoperitoneum formation, maintenance and extubation. These are the times when maximum surge in sympathetic drive is usually seen. Similar results were observed by Srivastava et al [5] and Zuberi et al [8] where dexmedetomidine was more effective than esmolol in preventing such responses in laparoscopic cholecystectomy.

In our study, HR never exceeded baseline at any time points. Two patients in group E showed surges in blood pressures >20% of baseline at pneumoperitoneum formation. Both dexmedetomidine and esmolol succeeded their intent in attenuating hemodynamics throughout surgery. Bhattacharjee et al [9] also, observed that both drugs effectively attenuated haemodynamic response during and after pneumoperitonium, however, no significant intergroup difference was seen.

Dexmedetomidine has long been known for its analgesic action.[10] Various studies have demonstrated that intraoperative administration of esmolol may reduce postoperative analgesic requirements.[11] In our study, dexmedetomidine group had significantly reduced postoperative fentanyl consumption. Zuberi et al [14] similarly showed superior analgesic action of dexmedetomidine over esmolol in terms of lesser number of patients requiring rescue analgesics in postoperative period.

The frequency of patients developing side effects in our study were

more in group D, though the difference was not statistically significant. 8/50 patients developed bradycardia and 14/50 developed hypotension. The reason behind this bradycardia and hypotension is sympatholytic effect of dexmedetomidine mediated by its action on α2 receptors. Incidence of PONV was also less in esmolol group. Watts et al[11] showed 61% reduction in PONV in patients who received esmolol compared with placebo. The reduction in PONV is probably an indirect consequence of opioid and volatile anesthetics sparing effect. There is some evidence that ß -blockade may have direct antiemetic effect.[15] Esmolol failed to contain the hypertensive response of pneumoperitonium in two patients while no such cases were seen in dexmedetomidine group.

Few studies have compared analgesic efficacy of esmolol and dexmedetomidine, but our study supersedes them because of use of IVPCA in postoperative period. PCA pump enabled us to quantify the exact requirement of postoperative fentanyl in both the groups. Limitations of this study were that time to extubation after stoppage of infusions and sedation in PACU were not evaluated.

CONCLUSION

Our study successfully concludes that both dexmedetomidine and esmolol can be used for hemodynamic maintenance in laparoscopic donor nephrectomy. However, intraoperative dexmedetomidine infusion lowers post-operative opioid requirement in comparison to esmolol.

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