Original Article

Comparative evaluation of dexmedetomidine and fentanyl in total intravenous anesthesia for laparoscopic cholecystectomy: A randomised controlled study

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Abstract

Background and Aims: Laparoscopic cholecystectomy is one of the commonly performed ambulatory surgeries. The selection of anesthetic agents for ambulatory surgeries should be done bearing in mind the need for early discharge. Opioids form an integral component of total intravenous anesthesia (TIVA) but their associated side effects may result in an increased hospital stay. Hence, we planned a study to compare the opioid (fentanyl) and non-opioid (dexmedetomidine) based technique of TIVA for laparoscopic surgery.

Material and Methods: Ninety ASA I and II patients between 18-60 years of either sex posted for laparoscopic cholecystectomy were randomly allocated into two groups namely group D (Dexmedetomidine) and group F (Fentanyl). Patients received propofol infusion along with group specific drug infusion, after which an appropriate size proseal laryngeal mask airway was placed. The patients were assessed for discharge time from post-anesthesia care unit (PACU), on table recovery time, time to first rescue analgesia, hemodynamic parameters, incidence of postoperative nausea and vomiting (PONV) and any other complication.

Results: Demographic profile of both the groups was comparable. Group D had longer on table recovery time (13.00 ± 2.34 min vs 6.29 ± 2.46 min; $P < 0.001$) and time to discharge from PACU (6.80 ± 3.96 min vs 2.36 ± 1.67 min; $P < 0.001$) compared to group F. Group F had better hemodynamic stability compared to group D. In group D, 77% patients required rescue analgesia in first one hour post surgery, unlike 22% in group F. No patient in group D had PONV.

Conclusion: Opioid based technique (Fentanyl) of TIVA is superior over non-opioid based (dexmedetomidine) technique with faster recovery, early discharge, decreased postoperative pain scores and better hemodynamic stability. PONV is observed with opioids which can be treated successfully with antiemetics.

Keywords: Dexmedetomidine, fentanyl, laparoscopic cholecystectomy, total intravenous anesthesia

Introduction

Laparoscopic cholecystectomy is a routinely performed day care surgery. Rapid recovery, adequate pain control and early discharge are the most important components of fast track anesthesia. Adequate perioperative analgesia facilitates early discharge following day care surgery. Opioids remain the drug of choice for perioperative analgesia but their associated side effects like respiratory depression, postoperative hyperalgesia, postoperative nausea and vomiting, ileus and urinary retention may delay the discharge resulting in increased hospital stay.[1] Post-operative pain following

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laparoscopic cholecystectomy is complex in nature and multimodal analgesia with non-opioid drugs have resulted in accelerated recovery.[2,3] Hence, there is continuous search for a non-opioid drug which is equipotent to opioids with minimal or no side effects.

Dexmedetomidine is a highly selective alpha-2 adrenoceptor agonist providing conscious sedation, analgesia and sympatholysis. It has been found that intravenous administration of dexmedetomidine during surgery results in decreased postoperative pain scores, nausea, vomiting and reduced requirement of rescue analgesia.[4-6] These properties of dexmedetomidine could be channelized in decreasing the use of opioids in clinical practice with improved recovery profile and reduced side effects. There have been studies where dexmedetomidine has been used as adjuvant to opioids for conduction of laparoscopic surgeries but to the best of our knowledge there is no published study where solely dexmedetomidine has been used along with propofol for TIVA in laparoscopic surgeries.

Hence, we hypothesised that non opioid based (Dexmedetomidine + Propofol) TIVA technique of anesthesia for laparoscopic cholecystectomy would result in early discharge from post-anesthesia care unit (PACU) with better hemodynamics and decreased side effects compared to opioid based (Fentanyl + Propofol) TIVA technique.

Material and Methods

This was a prospective randomised control study which was carried out in a tertiary care teaching institution over a period of one year after obtaining approval from the institutional ethics committee and written informed consent from the patient after explaining them about the objective of the study, the technique and its related complications.

The primary outcome of our study was time to discharge from post-anesthesia care unit on attainment of post-anesthesia discharge scoring system (PADSS) score of ≥9 using non-opioid based TIVA technique compared with opioid-based TIVA technique of general anesthesia for laparoscopic cholecystectomy. In the previous study conducted by Bakan M *et al.*,[7] the PACU discharge time using non-opioid based technique of TIVA (dexmedetomidine + lidocaine) was 10 (10-15) minutes, compared to 15 (15-20) minutes using opioid based (remifentanil) technique of TIVA.

Based on this previous study, in order to have power of study of 80% and Type 1 error <0.05 in our study, forty patients would be required in each study group. Considering the probability to lose some of the patients during follow-up (attrition of 10%), we took forty five patients in each study group. A total of 90 ASA I-II patients between 18-60 years of age of either sex, BMI ≤30 kg/m^2, posted for laparoscopic surgery with expected surgical duration of less than one and half hour were included in the study.

We excluded patients on anti-hypertensive drugs, anticipated difficult airway, history of substance abuse or on psychotropic drugs, known allergy to any of the study drugs, pregnant and lactating women from our study.

The patients were divided into two groups, namely, Group D (Dexmedetomidine) and Group F (Fentanyl) with the help of computer-generated random number table. Subsequently, the number slips were placed in opaque envelopes and sealed. The final group allocation was performed just before the procedure by opening the opaque sealed envelope by the staff nurse present. The anesthetist who prepared the study drug was blinded to group allocation.

All the patients underwent a thorough preoperative examination and were kept nil per oral as per the standard ASA guidelines. Anxiolysis was done with alprazolam 0.5 mg orally. On the day of surgery, written anesthesia consent was obtained. In the preoperative area after documenting the baseline vitals, an intravenous cannula (18G) was secured in the non-dominant hand and ringer lactate/normal saline was started. The patient was shifted to the operating room, placed supine and standard ASA monitors (Electrocardiography, pulse oximeter, noninvasive blood pressure) along with BIS electrode were applied. Oxygen was administered via facemask. According to the group allocation, the group specific study drug infusion was started. Patients in Group D received Inj. dexmedetomidine 1.0 μg/kg over 10 minutes followed by maintenance infusion at 0.5 μg/kg/hr intravenously. The patients in Group F received Inj. fentanyl 2.0 μg/kg over 10 minutes followed by maintenance infusion at 1.0 μg/kg/hr intravenously. After infusion of bolus dose of the study drug, anesthesia was induced with titrated doses of propofol (1-2 mg/kg IV) till the loss of verbal response and maintained at 150 μg/kg/min intravenously in all patients. After confirming the adequacy of ventilation, muscle relaxation was achieved and maintained with vecuronium bromide with the aid of neuromuscular monitoring. An appropriate size proseal laryngeal mask airway (PLMA) was inserted and the placement was confirmed. Cuff pressure and oropharyngeal leak pressure were recorded and maintained within standard limits. Patients were ventilated to maintain the $EtCO_2$ between 35-45 mm Hg and anesthesia was continued with 100% O_2 (air was not available in our setup) along with dexmedetomidine-propofol infusions in group D and fentanyl-propofol infusions in group F. The infusion rate of propofol was stepped up/down by 20 μg/kg/min so as to maintain Bispectral index (BIS) value between 40-60. Paracetamol 20 mg/kg was given intravenously to all patients

15 minutes after the skin incision. Hemodynamic parameters i.e., heart rate (HR), mean arterial pressure (MAP)) were recorded at fixed intervals starting from baseline value, after pre-anesthetic medication (PAM), after insertion of PLMA, at start of skin incision, beginning of carboperitoneum, thereafter every 2 minutes for next ten minutes and then every 5 minutes till the end of surgery. During surgery, any event of bradycardia (HR <60/min) was treated with Inj atropine 0.6 mg/kg IV. Hypotension (MAP <20% from baseline) was treated with incremental doses of Inj. mephentermine 6 mg IV along with a bolus of ringer lactate/normal saline. In case of persistent hypertensive episodes, it was advised to start nitroglycerine infusion and titrate it as per the requirement. Throughout the procedure, intra-abdominal pressure was maintained at ≤14 mm Hg and complete desufflation of the abdomen was ensured at the end of the surgery.

All infusions were stopped at the start of skin closure. Glycopyrrolate 10 mcg/kg and neostigmine 50 mcg/kg were administered intravenously to reverse the neuromuscular block after attaining train of four ratio (TOFR) ≥ 0.7. Nasogastric tube was removed after thorough suctioning. The PLMA was removed after patient became fully awake. On table, recovery time was recorded. Total propofol consumption (bolus and infusion) was also recorded. Patients were transferred to PACU and from the time of admission they were assessed every 5 minutes till they achieved a PADSS score ≥9. The person incharge of PACU was blinded to the group allocation of the patient. Post-operative pain scores were assessed using the 11-point numerical rating scale (NRS) where 0 corresponded to no pain and 10 to the worst imaginable pain. If NRS ≥4, rescue analgesia was provided with diclofenac 1.5 mg/kg intravenously. Time to first rescue analgesia was noted as well. PONV was if patient complained of nausea or had any episode of vomiting in PACU and was treated with ondansetron 0.1 mg/kg intravenously and the number of patient requiring anti-emetics was also recorded. All the postoperative parameters were recorded till the time the patient was not discharged from PACU.

The primary outcome of the study was the discharge time from PACU. The secondary outcomes were intraoperative hemodynamic variables (Heart rate, Mean arterial pressure), total propofol consumption, on table recovery time, time to rescue analgesia, number of patients requiring rescue analgesia in first hour postoperatively, the incidence of PONV and complications if any.

Discharge time from PACU (T1): Time between admissions to PACU till attainment of PADSS score ≥9.

On table recovery time (T2): Time taken from the stoppage of propofol infusion till the time patient starts responding to verbal command.

Time to first rescue analgesia (T3): Time between admissions to PACU till administration of first analgesic based on NRS score.

Statistical analysis

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. Nominal categorical data between the groups were compared using Chi-square test or Fisher's exact test as appropriate. For within the group comparison, Wilcoxon rank sum test was used for calculating significance of hemodynamic parameters at different time points from baseline. *P*- value <0.05 was considered statistically significant.

Results

A total of 90 patients fulfilling the inclusion criteria participated in the study. The demographic profile (age, sex, BMI, ASA physical status, duration of surgery) of the two groups were comparable [Table 1].

Intraoperative hemodynamic variables were found to be more stable in group F compared to group D as there were less fluctuations in the hemodynamic parameters intraoperatively. There was a statistically significant increase in the heart rate from the baseline, following PLMA insertion and after creation of carboperitoneum [Graph 1]. However, the difference was not statistically significant between the two groups. The difference in MAP between the two groups was statistically significant during major part of surgery starting from pre-anesthetic medication till 35 minutes following carboperitoneum ($P \leq 0.05$). On comparing the mean difference from the baseline, it showed that MAP was better controlled in group F as compared to group D, $P \leq 0.05$ [Graph 2]. The mean total propofol consumption was more in group D, however it was not statistically significant [Table 2].

The on table recovery time (T2) was significantly faster in group F compared to group D, $P \leq 0.001$ [Table 2]. The

Table 1: Comparison of demographic profile between the two groups

	Group D	Group F	*P*
Age (yrs)	36.13±10.12	35.53±10.10	0.832
Sex (M/F)	10/35	7/38	0.419
BMI (kg/m^2)	23.55±2.86	24.06±2.29	0.385
ASA (I/II)	43/2	41/4	0.677
Durationof surgery (min)	46.22±16.42	44.44±12.62	0.566

Table 2: Comparison of various parameters between the two groups

Parameter	Group D	Group F	*P*
Total propofol consumption (mg)	775.11±246.02	697.33±227.19	0.123
On table recovery time (T2 min)	13.00±2.34	6.29±2.46	<0.001
Time to 1st rescue analgesia (T3 min)	2.88±1.14	1.73±1.27	0.007
No. Of patients requiring rescue analgesia	33	10	<0.001
No. Of patients experiencing PONV	0	7	0.012

time to first rescue analgesia (T3) was significantly shorter in group D as compared to group F, $P \leq 0.001$ [Table 2]. The time to discharge from PACU (T1) was found to be significantly longer in patients of group D as compared to group F [Graph 3]. 77% patients in group D required rescue analgesia in the first hour post surgery unlike only 22% in group F [Table 2].

No patient in group D had PONV whereas 7 patients in group F required rescue antiemetic for treating it [Table 2]. No complications were noted in either of the two groups. All observations for the postoperative complications were noted till the time the patient was not discharged from PACU.

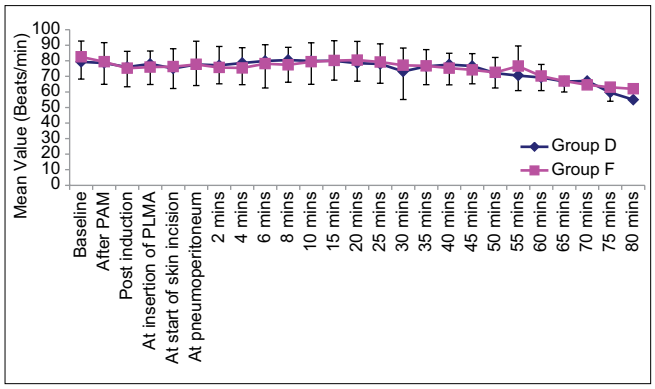
Discussion

Now is the era of ambulatory surgeries and laparoscopic cholecystectomy has out run its open counterpart as the treatment of choice for gallstones. The laparoscopic approach not only minimises the postoperative pain with rapid recovery but they also help to tide over the increasing patient load on the healthcare system by minimising the hospital stay. They are mostly preferred on day care basis necessitating the role of fast track anesthesia. General anesthesia is the gold standard for providing anesthesia for laparoscopic surgeries which can either be inhalation anesthesia or TIVA.[8] Until recently, inhalational anesthesia was the preferred method for administration of general anesthesia but even it also has its own drawbacks and shortcomings. In the past, TIVA could not gain popularity because of the technical difficulties and the fears of the performers.[9] But with the advent of high technology infusion pumps and development of ultra-short acting drugs, TIVA has become one of the preferred methods of general anesthesia in day care settings.

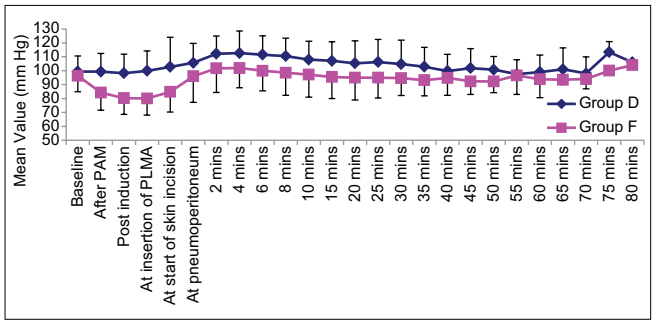
TIVA has many advantages over inhalational anesthesia such as no operating room pollution, minimal cardiac depression, less neurohumoral response, does not require sophisticated gas delivery systems and scavenging equipments, decreases the incidence of postoperative nausea and vomiting (PONV) and clear headed recovery.[10] Opioids have been extensively studied as an integral component of TIVA for perioperative analgesia. In the recent times non opioid based anesthesia is gaining popularity. Dexmedetomidine, a relatively newer drug, is a highly specific alpha-2 adrenergic receptor agonist which has been widely used as an adjuvant in laparoscopic surgeries. In addition to its sedative property, it may increase respiratory stability, decreases opioid need, provides analgesia, helps with early postoperative recovery, and maintains hemodynamics.[11-13]

Thus, we hypothesized that non-opioid based (dexmedetomidine) technique may be better than opioid based (fentanyl) technique of TIVA for laparoscopic cholecystectomy.

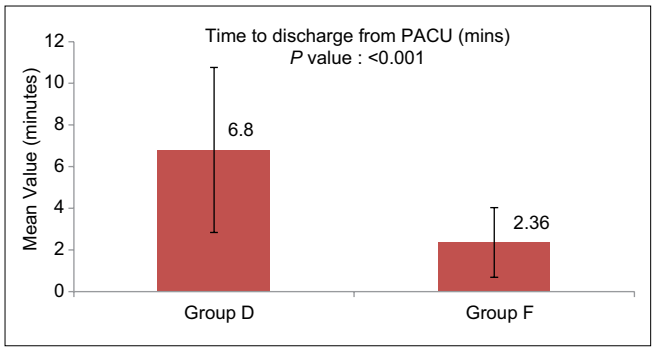
In our study, the primary outcome was the time to discharge from PACU which was significantly shorter with fentanyl compared to dexmedetomidine. Most of the delayed discharges in group D were due to prolonged sedation caused by dexmedetomidine as compared to fentanyl and its sedative effect got further enhanced when combined with propofol. The total propofol consumption was more in group D compared to group F which though was not statistically significant, but clinically this might have added to the reason for prolonged sedation in group D thereby delaying the time to discharge from PACU. Bakan M *et al.*[7] found similar results on comparing remifentanil with dexmedetomidine and lidocaine combination inspite of using lower dosage of dexmedetomidine compared to our study. But in their study the low dose of dexmedetomidine resulted in increased propofol consumption which was statistically significant and resulted in prolonged sedation and delayed discharge. Subasi H *et al.*[14] also found delayed recovery with dexmedetomidine despite administering it in low maintenance dose. However, at the time of induction of general anesthesia they supplemented opioid (fentanyl 1 mcg/kg) before endotracheal intubation. Perhaps the low maintenance dose of dexmedetomidine acted synergistically with opioid, thereby increased the time to discharge. Dexmedetomidine in higher doses cause profound sedation post-operatively, but even when used in lower doses with propofol or opioids, it acts synergistically with them to produce the level of sedation which is comparable to that produced at higher doses. The above stated reasons also helps us to justify the finding of significantly longer on table recovery time in patients of group D compared to group F of our study.



Graph 1: Comparison of heart rate between the two groups



Graph 2: Comparison of MAP between the two groups



Graph 3: Comparison between the time to discharge from PACU between the two groups

In our study, the time to first rescue analgesia was significantly shorter in group D compared to group F. Dexmedetomidine has mild analgesic property compared to opioids, however it has been successfully used as an alternative to opioids in various surgical procedures with reduced postoperative pain.[15-18] The intensity of postoperative pain is majorly dependent on the type of surgery. Though laparoscopic surgeries carry the advantage of reduced postoperative pain but laparoscopic cholecystectomy is unique in this context as there is significant sympathoadrenal response during the surgery with resultant increase in the demand of postoperative analgesia. In group D, 73% patients required rescue analgesia in the first hour of surgery, unlike group F where 22% of the patients required it because of the mild analgesia provided by dexmedetomidine. Both Bakan *et al.*[7] Subasi *et al.*[14] had contradictory results. They found that dexmedetomidine group had decreased postoperative analgesic requirements as compared to opioids. This may be due to the fact that both the studies have used remifentanil as the opioid which is an ultra-short acting drug whereas we have used fentanyl as the opioid in our study.

In our study, the mean heart rate was statistically comparable throughout the procedure in both the groups. In group F, throughout the procedure MAP either remained unchanged or decreased, probably due to its synergistic action with propofol.[19] At the beginning of infusion, dexmedetomidine causes transient hypertension before inducing hypotension which could explain the initial increase in MAP in group D. Also, in our study, the infusion rates of both the study drugs were fixed and were not titrated according to the hemodynamics of the patient. No patient in either of the two groups required antihypertensives or vasopressors intraoperatively. Bakan *et al.*[7] found more hypertensive episodes with dexmedetomidine infusion and 11 patients required nitroglycerine infusion intraoperatively. However, we attained better hemodynamics than Bakan *et al.*[7] in dexmedetomidine group probably because of higher infusion dosage and also we used PLMA as airway device unlike endotracheal tube used in their study. Subasi *et al.*[14] also found better hemodynamics stability with opioids compared to dexmedetomidine and did not require antihypertensives intraoperatively.

In our study, the incidence of PONV was significantly higher with fentanyl where 7 patients required rescue antiemetic unlike none in group D. Inspite of the higher incidence of PONV with opioids, the patients had early discharge compared to group D because the PONV was well taken care with rescue atiemetics. PONV is a known side effect with the use of opioids. Though there was an increased incidence of PONV with fentanyl, it was treated easily with use of $5HT_3$ receptor antagonist alone or with combination with dexamethasone. Bakan *et al.*[7] and Subasi *et al.*[14] also found similar results. It is seen that around 50% of patients who receive opioids as part of analgesia suffer from postoperative nausea and vomiting.[20] No other complications were reported in either of the two study groups. The person-in-charge of PACU who observed the patients for postoperative complications was blinded to the group allocation of the patients.

Limitations of the study

Though a sample size of 90 gave the study a power of 80%, a larger sample population might have increased the statistical validation. We did not use target controlled infusion pumps due to their non-availability in our setup which might have helped in better titration of the study drug which might have affected the outcome of our study.

Conclusion

Opioid based (fentanyl) technique is better than non-opioid based (dexmedetomidine) technique of total intravenous anesthesia for laparoscopic cholecystectomy with better hemodynamic profile, faster recovery and decreased requirement of rescue analgesia. PONV is the only side effect which can be dealt successfully with wide array of anti-emetics without increasing the stay in PACU.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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