

# Total Intravenous Anesthesia In Laparoscopic Cholecystectomy: Comparison Of Butorphanol And Fentanyl

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## Abstract

**Background:** The study aimed to compare the analgesic efficacy and recovery characteristics of fentanyl and butorphanol as analgesic under TIVA (Total Intravenous Anesthesia) for laparoscopic cholecystectomy and find out the better combination along with propofol.

**Materials and methods:** Sixty patients of ASA grade I and II of either sex in the age group of 18-60 years undergoing laparoscopic cholecystectomy were allocated to one of the two groups of 30 each. Group I received inj. fentanyl in the doses of 2 µg/kg while patients in group II received butorphanol in doses of 25µg/kg. All the patients were induced with inj. propofol 2 µg/kg and intubated with 100 µg/kg Vecuronium. Anesthesia was maintained by oxygen and propofol. Intra-operative analgesic efficacy was measured by hemodynamic parameters (HR, MAP).

**Results and Conclusion:** Suppression of sympathetic response to laryngoscopy and intubation was better with butorphanol than fentanyl. The emergence time, recovery time and post operative sedation was less in the fentanyl group (group I) while post operative analgesia was more in the butorphanol group (group II). There was no evidence of nausea and vomiting in any of the two groups. We can conclude that butorphanol provides better analgesia with total intravenous anesthesia as compared to fentanyl.

## INTRODUCTION

Laparoscopic cholecystectomy combines the benefit of completely removing the gallbladder with the advantages of shorter hospital stays, more rapid return to normal activities, less pain associated with the small, limited incisions and less postoperative ileus compared with the open laparotomy technique. With the advancement in anesthesiology practice, the hospital stay has reduced. However, the basic requirements for anesthesia have not changed from "analgesia, anesthesia and muscle relaxation" (1).

The availability of intravenous sedatives/hypnotics with rapid onset, stable operating conditions, shorter recovery profiles along with newer, more potent analgesics and user friendly infusion delivery systems has facilitated the TIVA technique to a great extent for laparoscopic procedures.

Propofol has proven to be suitable as a hypnotic for TIVA technique providing rapid onset as well as rapid recovery of protective reflexes and of cognitive and psychomotor

functions. At the same time, it must be administered in combination with drugs fulfilling other components of anesthesia.

Out of all modalities available to relieve pain, systemic opioids stand atop. Opioids produce analgesia primarily as a result of their agonist effects on opioid receptors in the CNS. The physico-chemical properties of different opioids can result in difference in their pharmacokinetic, pharmacodynamic and side-effect profiles. Though, there are lots of studies including fentanyl as an adjuvant analgesic under TIVA technique, only very few studies have been done with butorphanol.

Butorphanol, a synthetic opioid derivative is a mixed agonist-antagonist with analgesic potency greater than morphine and pethidine(2). Butorphanol and its metabolites are agonist at kappa-receptor (3) and mixed agonist-antagonist at mu (µ) receptors. Butorphanol is available only in the parenteral form, thus better suited for acute pain relief.

Butorphanol unlike morphine exhibits a ceiling effect on respiratory depression<sub>(3)</sub>.

The aims and objectives of this study were to compare the analgesic efficacy as well as recovery characteristics of intravenous butorphanol with intravenous fentanyl, as an adjuvant analgesic to TIVA for laparoscopic cholecystectomy.

## **MATERIAL & METHODS**

After obtaining approval from hospital ethical committee and informed consent from the patients, sixty patients between the age of 20-60 years belonging to ASA grade I and II scheduled for elective laparoscopic cholecystectomy were studied. The patients were subjected to detailed clinical examination and routine investigations to exclude any associated systemic disorder.

**Exclusion Criteria:** The patients with systemic disease like, endocrine, respiratory, cardiac, hepatic or renal insufficiency and those having serum bilirubin >3.0 mg% as well as those cases where duration of anesthesia was more than a hour or any hypersensitivity to propofol, butorphanol or fentanyl were excluded from the study.

## **STUDY PROCEDURE**

All patients received tab alprazolam 0.5 mg (>40 kg) or 0.25 mg (<40 Kg) in the night before surgery and at 6 AM on the day of surgery. They were allocated to one of the two groups of 30 each.

- Group A: 30 Patients receiving 2ug/kg Fentanyl
- Group B: 30 Patients receiving 25ug/kg butorphanol

The patients were monitored for heart rate, ECG, SpO<sub>2</sub>, ETCO<sub>2</sub> and temperature, Urine output and baseline readings were recorded. Thereafter all patients were given injection glycopyrrolate 0.2mg, and fentanyl 2 µg/kg intravenously (Group A) or butorphanol 25 µg/kg (group B). After preoxygenating the patients with 100% oxygen for 3 minutes with facemask, all patients were induced with propofol 2 mg/kg and vecuronium bromide 100 µg/kg intravenously followed by tracheal intubation after full relaxation. Then patient's lungs were ventilated with O<sub>2</sub> flow of 8 L/min under IPPV and muscle relaxation was maintained with vecuronium bromide (1/5th of the intubating dose) by repeat dose as and when required. After induction, infusion of

propofol was started as a stepped-down scheme i.e. 10 mg/kg/hour for the first 10 minutes then

8 mg/kg/hour for the next 10 minutes followed by 6 mg/kg/hour till the end of surgery. Ringer's lactate as i.v. fluid was administered at the rate of 15 ml/kg in the 1st hour followed by 7.5 ml/kg/hr till the end of surgery to all patients.

Besides continuous monitoring of the above mentioned parameters, random blood sugar was estimated pre-operatively, 15 minutes following incision and 15 minutes following extubation from general anesthesia.

The value for ETCO<sub>2</sub> was kept between 35-45 mmHg intra-operatively. The infusion of propofol was stopped at the initiation of skin closure. Then all patients were reversed with neostigmine (50 µg/kg) with glycopyrrolate 10µg/kg followed by extubation of trachea as the patients started breathing spontaneously with eye opening on command.

The time-span between stoppage of propofol infusion and extubation of trachea was recorded as emergence time and the time span between extubation of the trachea and the time at which the patient could tell his/her name was recorded as recovery time.

All the patients were transferred to Post Anesthesia Care Unit (PACU) after the completion of satisfactory reversal. In the postoperative period any event of nausea and vomiting, blood sugar level, duration of sedation and the duration of analgesia (time interval between analgesic administration to the time when the patient complained of pain in PACU) were recorded.

The level of sedation in the postoperative period was observed using Ramsay sedation scores. Sedation scores were recorded once the patient was shifted to PACU and then every 15 minutes till 1 hour followed by every 30 minutes until the patient reached the sedation score of 2, which was considered to be the acceptable level of sedation as patients at this score were cooperative and tranquil.

## **STATISTICAL ANALYSIS**

The mean and standard deviation of the parameters studied during observation period were calculated for two treatment groups and compared using students 't' test. The critical value of 'p' indicating the probability of significant difference was taken as < 0.05 for comparisons.

## OBSERVATIONS & RESULTS

All the patients were statistically similar as regards age, sex and body weight (Table I).

### Figure 2

Table 2: The baseline mean heart rate in group I was  $82.37 \pm 8.99$  which was almost similar to group II ( $81.03 \pm 8.56$ ).

	Group I n=30	Group II n=30	t value	p value	Statistical Significance
Age in years	$37.73 \pm 7.31$	$36.73 \pm 7.31$	0.529	0.599	NS
Wt. in kg	$50.30 \pm 5.05$	$48.30 \pm 5.05$	1.533	0.131	NS

Pulse rate and mean arterial pressure (MAP) were recorded at the baseline (0), after induction (1), after endotracheal intubation (2), at the time of incision (3), 15 minutes after induction (4), 30 minutes after induction (5), 45 minutes after induction (6), after extubation of the trachea (7) and 5 minutes after tracheal extubation (8).

Hemodynamic parameters, statistical comparison between the two groups and also statistical comparison in the same group at different time intervals is as shown in

### Figure 3

Table 3: Hemodynamic data

Time Interval	Mean Heart Rate $\pm$ SD					Mean MAP $\pm$ SD				
	Group I n = 30	Group II n = 30	t value	p value	SS	Group I n = 30	Group II n = 30	t value	p value	SS
0 Base line	$82.37 \pm 8.99$	$81.03 \pm 8.56$	0.588	0.599	NS	$91.00 \pm 8.64$	$89.77 \pm 8.41$	0.560	0.577	NS
1 (Post ind.)	$74.83 \pm 8.86^*$	$76.10 \pm 8.29^*$	-0.572		NS	$76.00 \pm 8.64^*$	$78.87 \pm 8.64^*$	-1.293	0.201	NS
2 (Post Int.)	$78.17 \pm 8.82^{\#}$	$79.23 \pm 8.79$	-0.469	0.641	NS	$77.33 \pm 5.88^*$	$80.30 \pm 7.87^{\#}$	-1.764	0.083	NS
3 (Skin Inci.)	$79.67 \pm 8.83^{\#}$	$79.83 \pm 8.86$	-0.074	0.942	NS	$79.00 \pm 6.17^*$	$80.77 \pm 8.41^*$	-0.928	0.357	NS
4 (15 m after induction)	$78.83 \pm 8.86^{\#}$	$80.83 \pm 8.69^{\#}$	-0.882	0.381	NS	$76.90 \pm 6.08^*$	$79.77 \pm 8.41^*$	-1.513	0.136	NS
5 (30 m after induction)	$77.57 \pm 9.21$	$80.87 \pm 8.49^{\#}$	1.443	0.155	NS	$77.00 \pm 7.93^*$	$83.80 \pm 8.38^{\#}$	-3.229	0.002	SF
6 (45 m after induction)	$79.95 \pm 5.20^{\#}$	$82.00 \pm 4.44^{\#}$	-1.217	0.232	NS	$78.00 \pm 8.46^*$	$80.00 \pm 4.46^*$	-1.235	0.226	NS
7 (After Ext.)	$84.17 \pm 8.93^{\#}$	$83.67 \pm 8.76^{\#}$	0.219	0.827	NS	$82.47 \pm 7.37^{\#}$	$84.80 \pm 8.40^{\#}$	-1.143	0.258	NS
8 (5Min after Extubation)	$86.03 \pm 8.82^{\#}$	$85.90 \pm 8.92^*$	0.058	0.954	NS	$81.00 \pm 7.97^{\#}$	$85.77 \pm 8.41^{\#}$	-2.253	0.028	SF

\* Statistically significant within the group as compared to base line i. e. 0 Time interval

# Statistically significant within the as compared to post induction level i.e. 1 Time Interval

NS Statistically Not significant

SF Statistically Significant

### Figure 4

Table 4: Showing Duration of Anesthesia, Analgesia & Sedation

	Group I n=30	Group II n=30	t value	p value	Statistical Significance
Duration of Anesthesia (Min)	$46.73 \pm 7.00$	$44.73 \pm 7.80$	1.105	0.774	NS
Duration of P O Analgesia	$60.32 \pm 6.97$	$129.69 \pm 25.81$	-14.20	0.000	Significant
Duration of P O Sedation	Nil	$1.19 \pm 0.62$	10.54	0.000	Significant

There was no statistically significant difference between the two groups throughout the study period, while on comparison within the group I heart rate decreased significantly post induction  $74.83 \pm 8.86$  per min (Time interval 1v/s 0). The heart rate decreased at time interval 2, 3, 4 and 6 as  $78.17 \pm 8.82$ ,  $79.67 \pm 8.83$ ,  $78.83 \pm 8.86$ ,  $79.95 \pm 5.20$ , and increased at 7 and 8 as  $84.17 \pm 8.93$  and  $86.03 \pm 8.82$  respectively. In group II on comparison within the group the heart rate decreased significantly after induction at time interval 1 ( $76.10 \pm 8.29$ ) as compared to baseline ( $81.03 \pm 8.56$ ). When statistical comparison was made between time interval 1 and rest, there was a significant decrease in pulse rate at time interval 4 and 5 ( $80.83 \pm 8.63$  and  $80.87 \pm 8.49$ ) and significant increase at time interval 6, 7 & 8 ( $82.00 \pm 4.44$ ,  $83.67 \pm 8.74$  and  $85.90 \pm 8.92$ ) respectively.

The mean arterial pressure in group I was  $91.00 \pm 8.64$  which was similar as  $89.77 \pm 8.74$  in group II at 0 time interval. On comparison with group II the MAP increased and it was statistically significant at time interval 5 and 8 ( $77.00 \pm 7.93$  v/s  $83.80 \pm 8.38$  &  $81.00 \pm 7.97$  v/s  $85.77 \pm 8.41$  respectively). On statistical comparison within group I, the MAP decreased significantly at time interval 1, 2, 3, 4, 5, 6, 7 and 8 ( $76.00 \pm 8.64$ ,  $77.33 \pm 5.88$ ,  $79.00 \pm 6.17$ ,  $76.90 \pm 6.08$ ,  $77.00 \pm 7.93$ ,  $78.00 \pm 8.46$ ,  $82.47 \pm 7.37$ ,  $81.00 \pm 7.97$ ) respectively. On comparison of MAP at time interval I and rest MAP was significantly increased at time interval 7 & 8 ( $82.47 \pm 7.37$  &  $81.00 \pm 7.97$  respectively).

On comparison within group II MAP showed significant increase as compared to baseline ( $78.87 \pm 8.64$  v/s  $89.77 \pm 8.41$ ). The MAP showed significant increase at time interval 5, 7, 8 when compared to time interval 1 ( $83.80 \pm 8.38$ ,  $84.80 \pm 8.40$  and  $85.77 \pm 8.41$ ) respectively.

The duration of anesthesia in group I was  $46.73 \pm 7.00$  which was almost similar as in group II ( $44.73 \pm 7.80$ min).

The duration of analgesia was significantly more in group II

in comparison to group I ( $129.69 \pm 25.81$  v/s  $60.32 \pm 6.97$  min) respectively.

The duration of post-operative sedation in group II was significantly more than group I ( $1.19 \pm 0.62$  v/s nil) Table III.

## Figure 5

Table 5: Showing Emergence & Recovery time

	Group I n=30	Group II n=30	t value	p value	Statistical Significance
Emergence Time	$4.24 \pm 1.04$	$5.31 \pm 0.89$	-4.092	0.00	Significant
Recovery Time	$1.24 \pm 0.18$	$2.00 \pm 0.61$	-6.545	0.00	Significant

The emergence time in group I was significantly less than group II ( $4.24 \pm 1.04$  v/s  $5.31 \pm 0.89$  min) respectively. The recovery time in group II was significantly more in comparison to group I ( $2.00 \pm 0.61$  v/s  $1.24 \pm 0.18$  min) respectively.(Table IV)

## Figure 6

Table 6: Showing Mean Random Blood Sugar:

Time Interval	Group I n=30	Group II n=30	t value	p value	Statistical Significance
0	$89.00 \pm 10.97$	$89.00 \pm 10.69$	-1.550	0.132	NS
1	$90.90 \pm 6.27$	$94.57 \pm 13.28$	-5.067	0.000	Significant
2	$100.10 \pm 13.61$	$94.17 \pm 13.49$	4.777	0.000	Significant

The baseline random blood sugar was almost similar in both the groups. It was significantly more in group II in comparison to group I at time interval 1 ( $94.57 \pm 13.28$  v/s  $90.90 \pm 6.27$ ) and it was significantly less in group II as compared to group I at time interval 2 ( $94.17 \pm 13.49$  v/s  $100.10 \pm 13.66$ ) respectively Table V.

{image:6}

## DISCUSSION

Pandit and Kothary<sup>(4)</sup> compared fentanyl with butorphanol for outpatient laparoscopic procedures. They concluded that butorphanol gives better protection against sympathetic stimulation to tracheal intubation. There was no other significant difference between butorphanol and fentanyl during either induction or maintenance of anesthesia.

Billard et al<sup>(5)</sup> conducted a study to find out the hemodynamic response to induction and intubation with propofol and fentanyl. They stated that fentanyl adds to the hemodynamic suppression effect of propofol during induction and tracheal intubation.

Bhavsar et al<sup>(6)</sup> found intravenous fentanyl in a dose of 2 µg/kg to be safe and effective in controlling laryngoscopy and intubation response.

In the present study, as shown in Table II, there was a significant decrease in mean pulse rate from the baseline following induction in both the groups. The intubation response was cut down by both the drugs equally. Throughout the procedure the change in pulse rate from the baseline value was statistically insignificant in both the groups.

On comparing the mean pulse rate of the two study groups using unpaired 't' test there was no significant difference between fentanyl and butorphanol starting from induction to maintenance and recovery.

Again though there was a significant fall in mean MAP after induction in both groups (shown in Table III), both fentanyl and butorphanol were able to stabilize and maintain the MAP close to the post-induction level throughout the procedure (Table III).

When we compared the change in mean MAP between the two study groups using unpaired 't' test both groups were comparable. Thus, we noticed no significant difference between fentanyl and butorphanol in maintaining hemodynamics under TIVA technique, which is in agreement with the study findings reported above.

It is a well known fact that propofol causes significant myocardial depression and fall in MAP. When combined with fentanyl or butorphanol, this fall was greater and both the combinations were effective to suppress the intubation response. As glycopyrrolate was added to the premedication which may cause tachycardia the combination of propofol with fentanyl or propofol with butorphanol was still able to decrease the pulse rate though minimally.

In measuring the mean random blood sugar (RBS) we observed no difference in the baseline, intraoperative and postoperative values in between two groups. This corroborates nicely with the findings of hemodynamic parameters. There was a significant rise in postoperative blood sugar level from the baseline level in the fentanyl group in contrast to the butorphanol group, which may be explained by the wearing effect of fentanyl (Table V).

The emergence time (i.e., the time period from stoppage of propofol infusion to extubation of trachea) in the fentanyl

group was significantly lesser than that of butorphanol group. This explains that the butorphanol group patients take more time to be extubated than the other group (Table V).

Till date there is no study that simulates this finding but Jenstrup et al<sup>(7)</sup> conducted a comparative study between fentanyl and alfentanil for TIVA along with propofol. They found the emergence time to be 10 minutes and recovery time 3 minutes in the fentanyl group whereas 11.5 minutes and 1.8 minutes in the alfentanil group respectively.

In the present study the recovery time, in the fentanyl group was significantly lesser to that of butorphanol group as shown in Table V.

Del<sup>(8)</sup> found the duration of analgesia provided by intravenous butorphanol to be about 2 hour (0.5 mg dose) or 2-4 hours (1-2 mg dose). Lippman et al<sup>(9)</sup> conducted a double blind study on intravenous butorphanol and concluded the duration of action to be at least 60 minutes.

In the present study, we found the mean duration of analgesia provided by fentanyl 1 hour, to be significantly of shorter duration to that of butorphanol 2 hours.

The duration of sedation in the butorphanol group was significantly higher than that of fentanyl group. Many studies have reported sedation to be the most common adverse effect associated with butorphanol. The frequency ranges from 30-40% although one study by Lippman et al<sup>(9)</sup> found an incidence of 88%. Though during recovery this effect may be advantageous, this may explain the delayed emergence and recovery in this group compared to the fentanyl group

In this study, the incidence of postoperative sedation was 100% and sedation is concluded to be an unavoidable side effect of butorphanol when given in adequate doses.

The incidence of PONV is decreased when propofol is administered, regardless of the anesthetic technique<sup>(10)</sup>. When administered to induce and maintain anesthesia, it is more effective than ondansetron in preventing PONV<sup>(11)</sup>. It is possible that propofol modulates subcortical pathways to inhibit nausea and vomiting or produces a direct depressant effect on the vomiting centre.

Phillips et al<sup>(12)</sup> conducted a comparative study between TIVA with propofol and inhalational anesthesia with isoflurane for major abdominal surgeries. They noticed

significantly less nausea (15.4%) in the propofol group than in the isoflurane group (33.7%) for the first two hours but not thereafter.

Morimoto et al<sup>(13)</sup> conducted a study on TIVA with propofol and fentanyl and compared it to the general anesthesia with thiopentone nitrous oxide in oxygen and isoflurane anesthesia. They concluded a lower incidence of nausea in the TIVA group but no difference was found in the incidence of vomiting.

Vijayaraghavan<sup>(14)</sup> compared TIVA versus general anesthesia and found an incidence of nausea (10.1%) and vomiting (6.1%) in TIVA patients whereas 18% and 9% in the general anesthesia patients respectively.

In the present study, we observed no incidence of nausea, vomiting or nausea with vomiting in the postoperative period. This may be due to the reason of shorter observation period in PACU in our study.

## CONCLUSION

We conclude that butorphanol provides better analgesia with total intravenous anesthesia as compared to fentanyl.

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