International Journal of Medical Anesthesiology

E-ISSN: 2664-3774
P-ISSN: 2664-3766
www.anesthesiologypaper.com
IJMA 2023; 6(1): 99-103
Received: 02-11-2022
Accepted: 16-12-2022

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A comparative evaluation of butorphanol, fentanyl and nalbuphine for total intravenous anaesthesia in laparoscopic cholecystectomy

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DOI: https://doi.org/10.33545/26643766.2023.v6.i1b.378

Abstract
Introduction: The study compared the effectiveness of opioids: butorphanol, fentanyl and nalbuphine as a part of Total Intra Venous Anaesthesia (TIVA) using propofol as an inducing agent in all three groups in laparoscopic cholecystectomy in view of haemodynamic stability, analgesia and recovery characteristics.
Aims: To compare the efficacy of opioids *viz*. butorphanol, fentanyl and nalbuphine as a part of TIVA using propofol as an inducing agent in all the three groups in laparoscopic cholecystectomy in view of Haemodynamics variables, analgesia and recovery characteristics.
Material and Methods: This randomised prospective study was conducted in ninety patients of ASA grade I of either sex, in the age group of 20- 60 yrs and weighing 30- 70 kg undergoing laparoscopic cholecystectomy. Patients in group I received 25 µg/kg of inj. butorphanol intravenously, group II received 2 µg/kg of inj. fentanyl intravenously and group III received 0.3 mg/kg of inj. nalbuphine intravenously just before induction of anaesthesia. Induction was carried out exclusively with IV agents with inj. propofol 2 mg/kg and inj. vecuronium bromide 100µg/kg intravenously. Anaesthesia was maintained with TIVA using propofol infusion according to the Bristol infusion regimen and intermittent top-up doses of muscle relaxant. Haemodynamic monitoring, recovery characteristics in form of emergence time and recovery time, duration of analgesia, sedation and any side effects were recorded.
Results: In our study, it was found that butorphanol maintained a better steady state of haemodynamics throughout the intraoperative period as compared to fentanyl and nalbuphine. The attenuation of pressor response was again better with butorphanol, although fentanyl also suppressed this response to some extent. In view of recovery parameters, butorphanol and nalbuphine showed slow recovery in comparison to fentanyl whereas butorphanol provided better analgesia than the other two drugs.
Conclusion: To conclude, the study demonstrated the agonist-antagonist type of opioids can be a suitable alternative to the scheduled agonist opioids like fentanyl.

Keywords: Analgesia, butorphanol, fentanyl, nalbuphine, laparoscopic cholecystectomy

Introduction

TIVA is the next step in the evolution of the concept of balanced anaesthesia which obviates the need for an inhalational agent while maintaining the anaesthetic state with the use of short-acting intravenous drugs alone [1]. Basic principles of anaesthesia remain the same and involve achieving the four elements of a balanced technique of general anesthesia [2]; Block of mental, reflex, sensory and motor functions. However, no individual intravenous agent can fulfil all four basic components with an acceptable margin of safety.

To achieve the desired elements of balanced anaesthesia, TIVA entails the use of multiple drugs to address different elements of balanced anaesthesia with anaesthesia, analgesia and muscle relaxation.

For TIVA, propofol has shown to be an effective hypnotic. It has a pharmacokinetic profile that suited TIVA because the combination of high lipid solubility, shorter context-sensitive half-life and rapid clearance ensures plasma levels fall rapidly even after long infusions. The incidence of Post-Operative Side Effects: Sedation, Nausea and Vomiting (PONV) is decreased when propofol is administered regardless of anaesthetic technique [3]. But alone it is not a complete anaesthetic to address all the components of balanced anaesthesia.

Opioids are group of drugs which can be used to supplement TIVA, to address its analgesic component. They not only minimise requirements for potent anaesthetic agents during induction and maintenance but also provide more complete recovery from anaesthesia without unduly prolonging it [4].

When used together, opioids have a synergistic effect that significantly lowers the dosage of propofol and other sedative-hypnotics needed to induce unconsciousness and to counteract unpleasant stimulation such as skin incision [5]. Heart rate responses to laryngoscopy are better controlled with an opioid than with esmolol [6]. Short-acting narcotics agents such as fentanyl are often used for this purpose. However, these agonists can lead to adverse effects like respiratory depression, dizziness, nausea and vomiting as well as abuse potential leads to their limited availability.

This study aimed to evaluate the efficacy of an agonist-antagonist type of opioids as an adjuvant to propofol-based TIVA, thereby replacing the agonist opioids which have higher side effect profiles and abuse potential, moreover, being scheduled drugs that are not freely available.

Material and Methods

This prospective randomised study was conducted in the department of anaesthesia and intensive care, at a tertiary centre after getting approval from the hospital's ethical committee. Ninety patients belonging to the American Society of Anaesthesiology (ASA) grade I of either sex in the age group of 20- 60yrs and weighing 30-70 kg were included in this study.

Patients with systemic diseases like endocrine, respiratory, cardiac, hepatic or renal insufficiency, serum bilirubin > 3.0mg%, duration of anaesthesia more than 90 minutes, patients with a history of any hypersensitivity to propofol, butorphanol, fentanyl or nalbuphine and patients in whom the surgery was converted into conventional open cholecystectomy were excluded from the study.

A routine pre-anaesthetic evaluation of patients undergoing study was performed a day before surgery with special reference to basic demographic characteristics, general and systemic physical examination and routine investigations. They were randomly divided into three groups with the help of a computer-generated table of random numbers.

Group I received 25µg/kg of inj. Butorphanol intravenously.

Group II received 2µg/kg of inj. Fentanyl intravenously.

Group III received 0.3mg/kg of inj. Nalbuphine intravenously.

In the operation theatre, all the patients were given inj. glycopyrrolate 0.2mg intravenously, along with the study drug after recording baseline vitals just before induction. The patients were preoxygenated with 100% oxygen for 3 minutes and then induced with inj. propofol 2mg/kg and inj. vecuronium bromide 100 µg/kg intravenously. This was followed by tracheal intubation after full muscle relaxation and patients were ventilated with 50% oxygen in air under IPPV. Soon after induction, an infusion of 1% solution of propofol was started according to the Bristol infusion regimen[7] based on lean body weight i.e., 10 mg/kg/hr for the first 10 minutes, followed by 8 mg/kg/hr for the next 10 minutes and then followed by 6mg/kg/hr through a controlled infusion system till the end of the surgery. Muscle relaxation was maintained with top ups of inj. vecuronium bromide (1/5th of the intubating dose) as and when required. A nasogastric tube was placed, and a laparoscopic procedure was carried out in standard fashion. IAP was maintained between 10-12 mmHg. Infusion of propofol was stopped at the start of skin closure. At the end of the procedure, neuromuscular blockade was antagonised by inj. glycopyrrolate 8µg/kg and inj. Neostigmine 50µg/kg intravenously followed by extubation of the trachea when the patient started breathing spontaneously with eye-opening on command.

Intraoperatively, haemodynamic parameters including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded. A continuous record of SpO_2, ECG and $ETCO_2$ was done. The time when propofol infusion was stopped and patient extubated was recorded as EMERGENCE TIME [8] and the time between the extubation of the trachea and when the patient told his/her name was recorded as RECOVERY TIME [8]. The SpO_2 and $ETCO_2$ were kept between 98-100% and 35-45 mmHg respectively throughout the intraoperative period.

After completion of satisfactory reversal, patients were shifted out of the operation theatre and in the postoperative period following parameters were recorded:

Duration of postoperative sedation: The Modified Ramsay Sedation Scoring System was used to measure the level of sedation in the postoperative period. Sedation scores were taken starting when the patient was transferred to the recovery ward, then every 15 minutes for the next hour, then every 30 minutes, until the patient reached a sedation score of 2, which was the acceptable level of sedation because the patient was calm and cooperative at this point.

Duration of analgesia was recorded as the time between the analgesic administration at induction till the time the patient demanded analgesia in postoperative period. Rescue analgesia was given with inj. tramadol 1mg/kg i/v SOS. Any incidence of postoperative nausea and vomiting was recorded in the recovery room.

Statistical Analysis

Sample Size: Study done by Verma R K, Jaiswal S *et al*. Recovery time were 1.24±0.81 and 2.00±0.61 with fentanyl and butorphanol, respectively. Our estimated sample size based on Recovery time among groups. For the sample size calculation, we have defined mean difference of 0.76 with 1.01 Standard Deviation. We have calculated sample size with 95% confidence interval, 80% power and alpha level of 0.05.

Standard deviation and mean are used to present data. A one-way analysis of variance (ANOVA) was used to evaluate the statistical significance between the groups. Using the Bonferroni's t-test, post hoc intergroup statistical significance was assessed. Statistical significance was defined as a p-value of 0.05 or lower.

Observations and Results

Table 1: Showing Demographic Parameters

Group Parameters	Group I (Mean + SD)	Group II (Mean + SD)	Group III (Mean + SD)	ANOVA		Statistical significance
				f-value	p-value	
Age (years)	38.33+10.1	37.26+10.26	39.36+9.39	0.334	0.716	NS
Weight (kg)	58.5+8.14	58.3+8.20	61.36 +6.5	1.498	0.229	NS
Sex (M: F)	14:16	13:17	12:18	Chi-square test		NS
				f-value 0.27	p-value 0.087	

The groups were comparable in terms of age, weight and sex distribution

Table 2: Showing mean heart rate and mean arterial pressure: comparison using ANOVA

Group Intervals	Mean heart rate + SD				Mean arterial pressure + SD			
	Group I	Group Ii	Group III	p-value	Group I	Group II	Group III	p-value
0 (baseline)	83.79+10.46	81.06+9.56	84.7+8.97	0.323	98.86+8.73	99.35+7.61	96.53+5.56	0.294
1 (postinduction)	73.17+9.54	71.3+7.76	72.46+8.17	0.695	78.24+9.27	79.41+7.66	78.95+7.31	0.856
2 (postinduction)	90.13+8.81	89.70+9.88	94.00+8.94	0.146	102.1+10.64	103.61+8.38	108.44+8.36	0.024 (SS)
3 (skin incision)	92.24+8.72	94.3+7.26	96.20+6.84	0.144	106.60+7.76	108.3+7 7.86	107.20+8.84	0.201
4 (15m after induction)	83.20+8.75	84.26+9.43	84.86+8.44	0.769	96.50+7.30	100.64+6.76	98.85+7.95	0.102
5 (30m after induction)	81.89+7.5	82.16+7.85	81.83+8.06	0.984	94.48+7.35	95.78+7.10	97.65+7.34	0.246
6 (45m after induction)	79.63+7.34	80.96+8.83	81.53+8.55	0.699	94.11+6.40	95.88+7.88	97.52+8.02	0.267
7 (6 m after induction)	79.78+8.71	80.61+10.71	82.53+8.55	0.632	95.17+7.38	97.33+6.91	97.61+6.38	0.519
8 (75m after induction)	77.75+9.10	81.00+6.4	83.00+8.48	0.508	97.86+8.81	97.2+7.68	96.87+8.00	0.927
9 (90 m after induction)	80.00+0	81.5+6.55	78.00+4.24	0.809	93.00+00	93.58+3.56	92.15+1.20	0.874
10 (after extubation)	92.17+8.75	95.78+8.14	97.1+6.69	0.049 (SS)	106.43+7.08	110.78+5.59	111.37+5.51	0.004 (SS)
11 (5m after extubation)	82.72+8.46	85.8+7.25	82.7+7.29	0.206	97.25+5.91	99.22+5.14	99.43+4.91	0.242

On comparison between the groups for MAP using ANOVA, no statistically significant difference was observed at intervals 0, 1, 3, 4, 5, 6, 7, 8, 9 and 11 with pvalue > 0.05. The MAP at intervals 2 and 10 (after intubation and after extubation) showed a statistically significant difference in between groups with p-value of < 0.05.

On comparing mean SBP, using ANOVA, the value at interval 2 (after intubation) showed a significant difference between groups with a p-value of <0.05. When Mean SBP was analysed for intergroup comparison with Bonferroni's t-test, the p-value was 0.041 between group I and II whereas it was 0.009 between group I and III which was statistically significant.

When comparing the groups for mean diastolic BP at interval 10 (after extubation) showed a significant difference between groups with a p-value of 0.003 (p<0.05). When mean diastolic BP was analysed using Bonferroni's t-test, it was found a p-value of 0.001 between group I and II as well as between group I and III, which was statistically significant.

Table 3: Showing duration of anaesthesia, analgesia and sedation

Group intervals	Group I	Group II	Group III	ANOVA		Statistical significance
				f-value	p-value	
Duration of anesthesia	61.63 10.76	+64.46+13.10	65.73+8.73	1.09	0.340	NS
Duration of analgesia	121.79 9.41	+70.93+8.20	155.56+18.09	336	000	HS
Duration of sedation	5.92 1.25	+0	12.71+6.73	70	000	HS

On comparing groups for a mean duration of anaesthesia (in minutes), no statistically significant difference was observed between groups with a p-value of >0.05.

The mean duration of analgesia (in minutes) showed highly significant differences on intergroup comparisons with a p-value of 000 using Bonferroni's test. Duration of sedation when compared using Bonferroni's t-test, p values were statistically significant.

Table 4: showing recovery characteristics: emergence time and recovery time

Group intervals	Group I (Mean + SD)	Group II (Mean + SD)	Group III (Mean + SD)	ANOVA		Statistical significance
				f-value	p-value	
Emergence time	4.61+0.16	3.68+0.88	5.26 +1.16	12.933	1.21E-05	HS
Recovery time	1.97+0.76	1.20+0.51	1.55 +0.75	9.402	0.0002	HS

When groups were compared for ET using Bonferroni's t-test a p-value of 0.011 was found between group I & II, 6.96E-06 was in between group II and III which was statistically significant, whereas it was 0.122 between group I & II which was not statistically significant.

On comparing the groups for RT (in minutes) using Bonferroni's t-test statistically significant difference was observed between group I & II with a p-value of 0.000118. There was no statistically significant difference observed between groups II & III as well as between group I & III.

Table 5: Showing Incidence of Post-Operative Side Effects: Sedation, PONV

Group Intervals	Group I	Group II	Group III	Chi square value	p-value	Statistical significance
Post-op Sedation	13/17 (42.9%)	0/30 (0%)	14/30 (46.2%)	19.37	0.0001	SS
Ponv	0	1/29	0	2.02	0.36	NS

The percentage of patients showing sedation in group I was 42.9% and those in group III was 46.2%. No patient was sedated in group II. There was only a single patient in group II who complained of nausea.

Discussion

TIVA offers many advantages over conventional inhalational techniques. The recent focus on the use of intravenous agents in clinical practice stems from the availability of agents with the advantages of the rapidity of onset, pleasantness of induction, absence of irritation to the respiratory tract, stable operating conditions, shorter recovery profiles along with newer, more potent anaesthetics, availability of user-friendly infusion delivery

systems, simplicity and the fact that a minimum of equipment and complicated apparatus is required to facilitate TIVA technique to a great extent for laparoscopic procedures.

In this study we evaluated the efficacy of butorphanol, fentanyl and nalbuphine as a part of TIVA using propofol in view of haemodynamics variables, analgesia, and recovery characteristics.

When comparing the trend of haemodynamic parameters within the individual group it has been observed that mean HR, MAP, mean SBP and means DBP demonstrated a uniform trend. The values decreased significantly from baseline at 0 intervals to the post-induction period at interval 1 followed by rising trend at intervals 2 and 3 (i.e., after induction and at skin incision). Thereafter, there was a progressive fall in the mean HR, MAP, mean SBP and mean DBP at intervals 4, 5, 6, 7, 8 and 9 indicating attainment of intraoperative haemodynamic stability followed by a rise in MAP at interval 10 (after extubation) which was soon followed by values returning near to baseline levels at interval 11 (5 minutes after extubation). Propofol causes significant myocardial depression, and this effect is responsible for the fall in the mean HR, MAP, mean SBP and means DBP after induction. When combined with fentanyl, butorphanol or nalbuphine, this fall was greater and hence the combinations were more effective in suppressing the intubation response.

TIVA has been increasingly used in different patient population. Neil S Morton [9] in 2013 ellaborated on TIVA technique in paediatric patient population. Similarily, study done by Abd-Elazeem Elbakry, Wesam-Eldin Sultan *et al*. [10] on TIVA using propofol and dexmedetomidine, demonstrated TIVA is a better anaesthetic regimen than inhalation anaesthesia. TIVA provided better postoperative recovery with fewer postoperative side effects and analgesic requirements.

The mean heart rate at interval 10 (just after extubation) showed a statistically significant difference with a p-value of 0.049. Although not statistically significant it has been observed that mean heart rates were recorded lowest in group I followed by group II and the highest in group III. Khan FA, Zaidi A *et al*. [11] found that the heart rate was significantly higher in the nalbuphine group as compared to the buprenorphine group. When compared to MAP, mean SBP and mean DBP in three groups intraoperatively, it was seen that nalbuphine demonstrates poor attenuation of pressor response in terms of rise in MAP both at intubation and extubation as compared to butorphanol. Fentanyl also showed a statistically significant rise in MAP than butorphanol at extubation. On contrary, A study done by Madhu S, Balarama Reddy P *et al*. [12] showed nalbhupine as effective as fentanyl in controlling haemodynamic response to laryngoscopic & laparoscopic stress. Weiss BM, Schmid ER *et al*. [13] found that norepinephrine levels remained significantly higher in the nalbuphine group than in the fentanyl group. Pandit SK, Kothary SP *et al*. [14] concluded that butorphanol protects against sympathetic stimulation during tracheal intubation and during extubation.

When comparing the mean duration of analgesia in our study, it was found that the duration of analgesia was significantly longer with nalbuphine (2.5 hrs) in comparison to butorphanol (2 hrs) which in turn has a longer duration of analgesia than fentanyl (1 hr). Therefore, fentanyl has the shortest mean duration of analgesia; in fact, many of the patients in this group complained of pain immediately after extubation and were then supplemented with inj. tramadol 1mg /kg intravenously SOS. Del *et al*. [15] found the duration of analgesia provided by intravenous butorphanol to be about 2 hours (0.5mg dose) or 2-4 hours (1mg dose).

On comparing ET, results indicated a longer emergence time for nalbuphine and butorphanol than fentanyl. When evaluated for RT, longer recovery time observed with butorphanol & nalbuphine than fentanyl. The results were contrary to those found in a study done by Jenstrup, Nielsen J *et al.* [16]. They found an emergence time of 10 minutes and a recovery time of 3 minutes in the fentanyl group which were longer than those seen in our study. Although slightly longer, the ET recorded by Verma R K, Jaiswal S *et al*. [8] for fentanyl was 4.24±1.04 and for butorphanol was 5.31±0.89, which approaches just near our study's results. The results of RT in our study were consistent with this study, which were 1.24±0.81 and 2.00±0.61 with fentanyl and butorphanol, respectively.

Postoperative side effect in form of sedation was observed in butorphanol and nalbuphine group the incidence being 42.9% and 46.2% respectively. However, the sedation scores were either 3 or 4 and patients were easily arousable. The frequency of sedation reported with butorphanol ranges from 30-40%, which is also consistent with our study. Pandit SK, Kothary SP *et al*. [14] reported a 44.4% incidence of drowsiness with butorphanol as compared to 16.6% seen with fentanyl. Hussein AE, Youssef *et al*. [17] reported more sedation in the nalbuphine group as compared to morphine. PONV was seen in single patient in the fentanyl group. No patient in the other two groups had such a complaint. Gan TJ, Ginsberg B *et al*. [18] demonstrated that propofol when used to induce and maintain anaesthesia, is more effective than ondansetron in preventing PONV. The studies done by Phillips, Mirakhur RK *et al*. [19], reported a low incidence of PONV with TIVA as compared to GA with conventional inhalation technique. So, use of propofol can be reason for low incidence of PONV in our study.

Hence, it was concluded that Butorphanol demonstrated a steady state throughout the intraoperative period and attenuated pressor response effectively. Moreover, the longer duration of analgesia, lack of dangerous side effects, low abuse potential and free availability makes this drug a suitable adjuvant to supplement TIVA. Nalbuphine showed slightly higher values of hemodynamic variables throughout the intraoperative period, but the longer duration of analgesia, low side effect profile & free availability of this drugs makes it a potential substitute for supplementation of TIVA. The dose recommended for supplementation of anaesthesia ranges from 0.3 - 3 mg /kg. In our study we used the lowest dosage, this can be the reason for poor hemodynamic stability seen intraoperatively. The use of high doses may provide better hemodynamic stability and prolonged analgesia. So, further studies are required to study its role in TIVA.

In terms of recovery characteristics, Recovery Time & Emergence Time, Butorphanol & Nalbhupine showed slower recovery than Fentanyl, but further studies are needed to verify this. Also owing to the potential benefits of these drugs a delay of minute or two can be overlooked.

In our study, we used lower doses of these drugs so, study can be done with higher doses, which may improve the duration of analgesia & haemodynamic effects. Also, we did not study the cost effectiveness of TIVA & study drugs

which is one of the important factor in considering use of TIVA in routine surgeries.

Conclusion

This study concluded that agonist-antagonist series of opioids has potential to replace agonists because of their long analgesia, low side effect profile, easy availability & no abuse potential. Agonists like Fentanyl on the other hand cannot be encouraged to supplement T1VA due to their side effects, abuse potential & limited availability for being scheduled drugs.

Acknowledgement: Nil

Conflict of interest: Nil

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How to Cite This Article
Rajput A, Jamwal A. A comparative evaluation of butorphanol, fentanyl and nalbuphine for total intravenous anaesthesia in laparoscopic cholecystectomy. International Journal of Medical Anesthesiology 2023; 6(1): xx-xx.