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Comparison of Fentanyl and Butorphanol for Propofol Injection Induced Pain Response

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Abstract
Propofol is one of the most preferred drugs used for induction of anaesthesia. Pretreatment with fentanyl as well as butorphanol have been used effectively for reduction of propofol injection induced pain response. The present study was done to compare the efficacy of fentanyl and butorphanol for attenuation of propofol injection induced pain response, perioperative hemodynamic parameters and postoperative complications among two study groups.
Material and methods
A prospective double blind randomized controlled trial was conducted in a tertiary care hospital in Lucknow over a period of one year. ASA status I or II, aged 16 to 60 years, undergoing laparoscopic surgeries of upto two hours duration under general anesthesia, after taking consent, were enrolled. The study drugs fentanyl (2mcg/kg) and butorphanol (40mcg/kg) were then administered in group A and group B respectively, and pain on injection of propofol, perioperative hemodynamic and postoperative complications were recorded.
Result
In Group A, majority of cases (66.7%) had VRS score 0 while remaining (33.3%) cases had VRS score 1.In Group B, majority (53.3%) had VRS score 1 while remaining had VRS score 2 (40.0%) and score 0 (6.7%) ($p<0.001$).Incidence of shivering was higher in Group B as compared to Group A (16.7% vs. 13.3%).Incidence of nausea and vomiting too was higher in Group B(23.3%) as compared to Group A(20%). Incidence of sedation was higher in Group B as compared to Group A, (26.7% vs. 10.0%) but all these difference were not statistically significant.
Conclusion
Fentanyl was found to be more efficacious to control propofol injection induced pain response than butorphanol. Side effects of premedication of both the drugs were almost similar.
Keywords: *Propofol induce pain, fentanyl, butorphanol*

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I. Introduction

Management of pain is an issue of great concern during the operative procedures using intravenous propofol as induction agent in general anaesthesia. Incidence of pain during induction of anaesthesia varies from 28%-90% [1].

The pharmacological techniques used to reduce the incidence of pain following propofol administration include use of ligocaine and tramadol to propofol[2], metoclopramide[3], butorphanol[4] or dexamethasone or thiopentone[5]. All have been tried with variable and sometimes conflicting results. Pretreatment with opioids has been shown to have analgesic benefit. Fentanyl is a short acting pure opioid, interacts predominantly with opioid mu-receptor but also binds to kappa and delta-type opioid receptors. It is commonly used for intraoperative and postoperative systemic analgesia. Butorphanol, a synthetic opioid, kappa-receptor agonist as well as a mu-receptor antagonist can also reduce pain during induction with IV propofol and has analgesic and sedative properties.

The present study was carried out with an aim to compare the efficacy of fentanyl and butorphanol for attenuation of propofol injection induced pain response between groups of study population.

II. Material and Method

After the approval of the hospital ethics committee, 60 adult patients of either sex, of ASA status I or II ,aged 18 to 70 years, undergoing elective surgeries under general anesthesia were studied in this randomized double blinded study protocol. The anticipated duration of surgery was up to two hours. The study spanned over a period of one year. Exclusion Criteria were –

1. ASA grade III and IV
2. Patients with history of hepatic and renal disorders
3. Patients with history of thrombophlebitis
4. Pregnant females
5. Non-consenting patients
6. Allergic to drug

In Group A (n=30), patients received 2 mcg/kg of fentanyl and in Group B (n=30), patients received 40 mcg/kg of butorphanol as pretreatment. After one minute of pretreatment, the patients were administered one-fourth of the total calculated dose of propofol (2mg/kg) over five seconds and then after ten seconds patients were asked about the pain intensity during the injection and it was recorded as per the Verbal Rating Scale (VRS) as explained to the patient before induction. After decreasing the level of consciousness, rest of the anaesthetic medication was injected. Perioperatively standard monitors were applied and baseline parameters were recorded.

Propofol injection induced pain was noted using a 4-point verbal rating scale (VRS)-

0 = no pain, 1 = mild pain, 2=moderate pain without grimacing, 3 =severe pain with facial grimacing.

Intraoperative hypotension was treated by small doses of vasopressor while heart rate <50/min was managed by appropriate doses of Atropine. Reversal was given at the end of surgery using neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. Complications like postoperative nausea, vomiting, shivering and sedation were noted.

Hemodynamic parameters and verbal rating scale were recorded perioperatively and results were analyzed by students T-test, paired T-test and chi-square test. Data were expressed as mean ± SD or percentage (p-value< 0.05 was considered statistically significant).

III. Observations and Result

Written informed consent was obtained from sixty adult patients fulfilling the inclusion criteria scheduled for surgery under general anaesthesia. Difference in mean age of patients ('t'=0.816; p=0.418) and duration of surgery of both groups was not found to be statistically significant. Difference in physical (ASA Grade) and demographic variables in patients of two groups were not found to be statistically significant ('t'=0.816; p=0.418).

All the baseline hemodynamic parameters i.e. heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure of patients of the two groups were found to be comparable.

Table 1: Between Group Comparison of Heart rate at different time intervals

Time	Group A			Group B			Student 't' test	
	N	Mean	SD	n	Mean	SD	't'	'p'
Intra-op.								
Baseline	30	82.47	12.95	30	84.07	9.10	-0.554	0.582
Before Induction	30	85.33	13.83	30	87.03	12.44	-0.501	0.619
Intubation	30	88.87	11.92	30	90.70	10.71	-0.627	0.533
5 min	30	88.97	11.72	30	85.97	11.06	1.020	0.312
10 min	30	84.60	11.13	30	84.93	12.76	-0.108	0.915
15 min	30	83.00	11.26	30	84.70	12.18	-0.561	0.577
30 min	30	82.83	8.96	30	84.50	12.61	-0.590	0.557
45 min	29	82.90	10.23	28	86.07	14.24	-0.969	0.337
60 min	19	85.95	11.04	14	81.93	9.99	1.075	0.291
90 min	9	87.22	11.70	7	82.43	8.56	0.908	0.379
120 min	9	90.11	15.42	5	85.00	11.25	0.647	0.530
150 min	4	82.50	7.51	2	97.00	0.00	-2.576	0.062
180 min	2	87.00	0.00	0	.	.		
Post-op.(po)								
15 min po	30	85.27	10.34	30	87.57	11.84	-0.801	0.426
30 min po	30	82.60	10.05	30	85.80	11.42	-1.152	0.254
45 min po	30	81.17	10.96	30	84.10	10.79	-1.044	0.301
60 min po	30	80.00	9.54	30	80.80	9.30	-0.329	0.743

Difference (84.07±9.10 vs. 82.47±12.95 per minute) in baseline heart rate between the two groups was comparable and not found significant at any of the periods of observation during intraoperative and postoperative period.

Table 2: Between Group Comparison of Systolic BP at different time intervals

Time	Group A			Group B			Student 't' test	
	N	Mean	SD	N	Mean	SD	't'	'p'
Intra-op.								
Baseline	30	131.67	13.69	30	125.20	12.07	1.940	0.057
Before Induction	30	131.27	17.65	30	127.30	13.86	0.968	0.337
Intubation	30	131.47	22.31	30	133.87	22.27	-0.417	0.678
5 min	30	119.57	19.81	30	122.87	18.44	-0.668	0.507
10 min	30	117.43	16.45	30	115.67	16.54	0.415	0.680
15 min	30	117.23	18.07	30	116.63	15.67	0.137	0.891
30 min	30	129.13	19.58	30	120.60	16.04	1.847	0.070
45 min	29	129.28	20.35	28	119.43	15.37	2.056	0.045
60 min	19	133.95	15.69	16	110.81	11.11	4.941	<0.001
90 min	9	122.67	12.16	7	109.14	12.95	2.146	0.050
120 min	9	121.11	13.96	7	111.71	12.53	1.395	0.185
150 min	4	112.50	12.15	2	105.00	1.41	0.821	0.458
180 min	2	108.50	0.71	0	.	.		
Post-op.(po)								
15 min po	30	134.97	12.75	30	132.83	12.45	0.656	0.515
30 min po	30	133.00	13.59	30	130.33	12.12	0.802	0.426
45 min po	30	127.57	11.75	30	128.53	10.83	-0.331	0.742
60 min po	30	127.50	13.29	30	125.17	10.51	0.754	0.454

Difference in baseline systolic blood pressure of both groups (131.67±13.69 mm Hg vs 125.20±12.07 mm Hg) was not found to be statistically significant. Difference in systolic blood pressure during intraoperative period among patients of the two groups was found to be statistically significant only at 45 minutes, 60 minutes and 90 minutes.

Table 3: Between Group Comparison of Diastolic BP at different time intervals

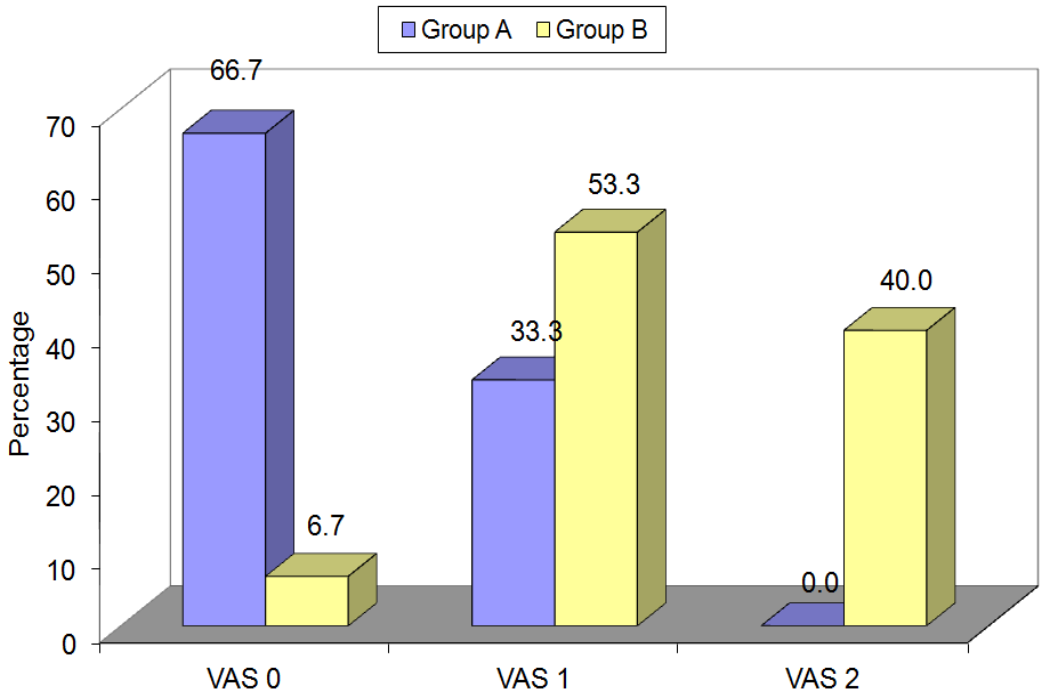
Time	Group A			Group B			Student 't' test	
	N	Mean	SD	n	Mean	SD	't'	'p'
Intra-op.								
Baseline	30	74.67	9.99	30	73.63	9.47	0.411	0.683
Before Induction	30	75.13	12.75	30	76.37	10.59	-0.408	0.685
Intubation	30	76.50	16.08	30	79.93	14.87	-0.859	0.394
5 min	30	69.57	12.03	30	72.80	16.05	-0.883	0.381
10 min	30	70.23	13.57	30	68.50	14.36	0.481	0.633
15 min	30	71.53	13.32	30	69.67	14.33	0.523	0.603
30 min	30	77.60	12.68	30	73.50	13.63	1.206	0.233
45 min	29	77.14	14.88	28	74.14	12.76	0.814	0.419
60 min	19	78.74	16.29	16	66.13	11.03	2.628	0.013
90 min	9	65.67	5.34	7	65.86	9.74	-0.050	0.961
120 min	9	66.89	6.58	7	66.00	8.10	0.242	0.812
150 min	4	68.50	1.29	2	65.00	1.41	3.055	0.038
180 min	2	61.00	1.41	0	.	.		
Post-op.(po)								
15 min po	30	79.67	9.66	30	80.57	8.38	-0.385	0.701
30 min po	30	77.53	9.19	30	78.47	7.64	-0.428	0.670
45 min po	30	76.90	9.76	30	79.17	9.21	-0.925	0.359
60 min po	30	76.40	9.59	30	77.13	9.99	-0.290	0.773

At baseline, difference in diastolic blood pressure of patients of Group A (74.67±9.99 mm Hg) and Group B (73.63±9.47 mm Hg) was not found to be statistically significant.
During intraoperative period, difference in diastolic blood pressure was found to be statistically significant only at 60 minutes (78.74±16.29 vs. 66.13±11.03 mm Hg) and 150 minutes (68.50±1.29 vs. 65.00±1.41 mm Hg).

Table 4: Between Group Comparison of Mean Arterial Pressure at different time intervals

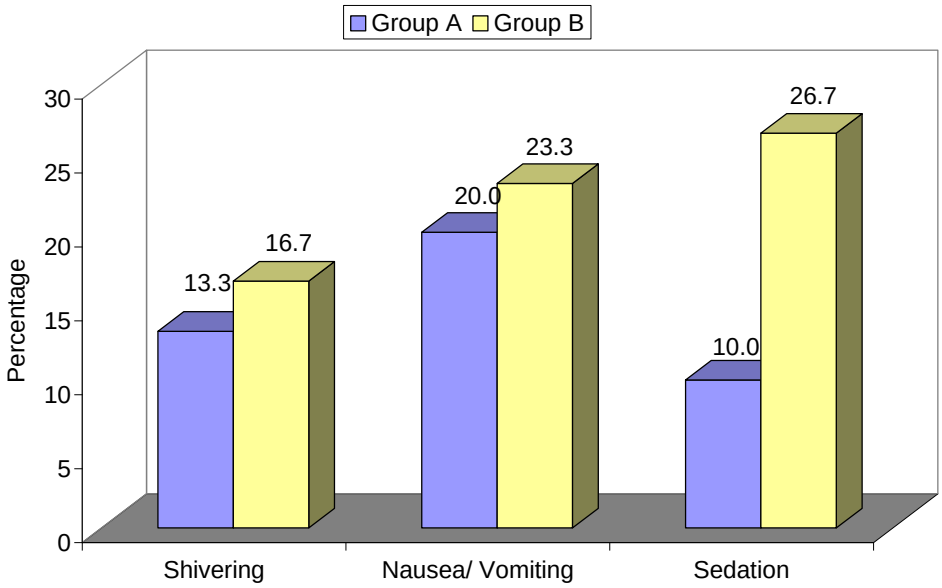
Time	Group A			Group B			Student 't' test	
	N	Mean	SD	n	Mean	SD	't'	'p'
Intra-op.								
Baseline	30	93.57	10.24	30	90.87	9.68	1.049	0.298
Before Induction	30	93.90	13.17	30	93.40	10.46	0.163	0.871
Intubation	30	94.87	17.65	30	97.87	16.06	-0.689	0.494
5 min	30	86.27	13.98	30	89.63	16.18	-0.862	0.392
10 min	30	85.97	13.55	30	84.27	14.28	0.473	0.638
15 min	30	86.77	13.45	30	85.40	14.07	0.385	0.702
30 min	30	94.77	14.08	30	89.10	13.94	1.567	0.123
45 min	29	94.45	15.44	28	89.25	12.74	1.384	0.172
60 min	19	97.21	15.10	16	81.06	10.10	3.642	0.001
90 min	9	84.67	6.22	7	80.43	10.47	1.012	0.329
120 min	9	85.11	8.68	7	81.14	9.01	0.893	0.387
150 min	4	83.00	3.65	2	78.00	1.41	1.782	0.149
180 min	2	77.00	1.41	0	.	.		
Post-op.(po)								
15 min po	30	98.13	9.54	30	98.10	7.74	0.015	0.988
30 min po	30	96.07	9.39	30	95.77	7.17	0.139	0.890
45 min po	30	93.77	9.46	30	95.77	8.15	-0.877	0.384
60 min po	30	93.43	9.79	30	93.17	8.94	0.110	0.913

Difference in mean arterial pressure of patients of both the groups was found to be comparable at all the periods of observation except at 60 minutes intraoperatively. Difference in mean arterial pressure of patients of the two groups was not found to be statistically significant at any of the periods of observation during postoperative period.



Graph 1: Comparison of propofol injection induced pain between two study groups
z=5.256; p<0.001 (Mann-Whitney U test)

In Group A, majority of cases (n=20; 66.7%) had VRS score 0 while remaining (n=10; 33.3%) cases had VRS score 1. On the other hand, in Group B, majority (n=16; 53.3%) had score 1 followed by those having score 2 (n=12; 40.0%) and score 0 (n=2; 6.7%) respectively. Statistically, the difference between the two groups was significant (p<0.001).



Graph 2: Between Group Comparison of Complications

Difference in Incidence of shivering, nausea vomiting and sedation in both the groups was not found to be statistically significant. None of the patients had any episode of hypotension or bradycardia.

IV. Discussion

Despite this favorable profile of propofol, the pain associated with its injection is cited to be the seventh most important problem by anaesthesiologists[6]. Fentanyl (2mcg/kg) and butorphanol (40mcg/kg) were used as premedication for the purpose of reduction in propofol injection induced pain response among patients scheduled to undergo elective surgery under general anaesthesia. To ensure that there is no induced bias owing to randomization, the age, gender, grade of surgery, anthropometry (weight, height and BMI), type of surgical procedure and baseline hemodynamic were also found to be statistically matched. As far as hemodynamic is concerned, both the drugs did not show any deleterious effect on hemodynamic (Ahire et al. 2016; Ray et al., 2011)**Error! Bookmark not defined.** . No significant difference between the two groups was observed at any time interval for heart rate and respiratory rate. There was no episode of bradycardia, tachycardia, respiratory depression, hypotension or hypertension in either of the two groups. In our study, majority of patients (n=20; 66.7%) in fentanyl group, did not experience pain, while only 10 (33.3%) patients experienced moderate pain; whereas in butorphanol group, only 2 (6.7%) patients did not experience pain, while majority (n=16; 53.3%) experienced mild pain and 12 (40%) patients experienced moderate pain. Basaranoglu et al.**Error! Bookmark not defined.** did not find fentanyl to be useful in control of propofol injection induced pain, this could be attributed to use of 1 mcg/kg dose of fentanyl instead of 2 mcg/kg dose used in the present study. Fujii and Itakura**Error! Bookmark not defined.** who used 50 mcg and 100 mcg fentanyl premedication found that while 50 mcg fentanyl did not prove to be beneficial, 100 mcg fentanyl was able to suppress the propofol injection induced pain effectively. Use of fentanyl at higher concentrations seems to bear fruitful results as has also been shown by other workers (Kizilcik *et al.*, 2015) **Error! Bookmark not defined.**. Use of butorphanol has also been reported to be effective at different dosages (Mahajan *et al.*, 2015)**Error! Bookmark not defined.**. The post injection pain caused by propofol includes both early as well as late pain. Early pain is attributable to phenolic nature of propofol whereas delayed pain is due to the release of mediators such a kininogen from kinin cascade**Error! Bookmark not defined.**.

The better response of fentanyl as compared to butorphanol observed in the present study could be attributable to its quicker onset of action as compared to butorphanol. In the present study, for both the groups, complications and side effects were limited. Statistically, there was no significant difference between the two groups with respect to complications and side effects.

V. Conclusion

On the basis of the study we conclude that efficacy of premedication of fentanyl or butorphanol for hemodynamic stability was almost similar but fentanyl was found to be more efficacious to control propofol injection induced pain response. Side effects of premedication of both the drugs (fentanyl and butorphanol) were

almost similar except incidence of sedation which was found to be more in butorphanol group though statistically insignificant.

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