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A COMPARATIVE STUDY OF INTRAVENOUS AND TRANSNASAL BUTORPHANOL AS AN ANALGESIC IN LAPAROSCOPIC CHOLECYSTECTOMY"

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ABSTRACT

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Key Words: Analgesia, Butorphanol, Laparoscopy. Laparoscopic cholecystectomy has revolutionized gallbladder surgeries and it has now become the "gold standard" of cholelithiasis. It offers many benefits than conventionalcholecystectomy, and has been promoted, as a"gentle surgery". Laparoscopic cholecystectomy combines the benefits of completely removing the gall bladder with the advantages of shorter hospital stays, more rapid return of normal activities, less pain associated with small limited incision and less postoperative ileus compared with the open laparotomy technique. However, this procedure is not risk free.In fact it produces significant hemodynamic changes. Pain is as old as human being and is becoming more and more troublesome to mankind with greater incidence of medical surgeries. Breaking the pain cycle at an early stage may prevent central sensitization and, consequently, chronic pain. A second objective is to improve surgical outcome with the goals of enabling early ambulation and recovery of gastrointestinal function which in turn reduce cardiopulmonary morbidity, psychological stress, anxiety and insomnia. Butorphanol is a synthetic opioid derivative possessing agonist-antagonist activity at opioid μ_2 -receptors and additional agonist activity at opioid -receptors. preventing a poor learned response to future pain episodes.

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INTRODUCTION

Laparoscopic cholecystectomy has revolutionized gallbladder surgeries and it has now become the "gold standard"of cholelithiasis. Peritoneal insufflation of CO_2 during most operations contributes to significant hemodynamic changes associated with laparoscopy. Pneumoperitoneum (Pnp) affects several hemostatic systems leading to alteration in acidbase balance, cardiovascular, pulmonary physiology and stress response. Despite considerable depth of anaesthesia, peritoneal CO_2 insufflation induced a significant and immediate increase in blood pressure and systemic vascular resistance, while end tidal CO_2 gradually increases and intraocular pressure rises. These hemodynamic changes may be detrimental for the patients so the drugs that prevent these changes can be. Pain is as old as human being and is becoming more and more troublesome to mankind with greater incidence of medical surgeries used. Breaking the pain cycle at an early stage may prevent central sensitization and, consequently, chronic pain. A second objective is to improve surgical outcome with the goals of enabling early ambulation and recovery of gastrointestinal function which in turn reduce cardiopulmonary morbidity, psychological stress, anxiety and insomnia; and preventing a poor learned response to future pain episodes. A wide area of postoperative pain management is covered by afferent neural blockade with local anesthetics. Next in order of effectiveness are high dose opioids, epidural opioids and clonidine, patient controlled opioid therapy and Non-Steroidal Anti-Inflammatory Agents. 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. Out of all modalities available to relieve pain, systemic opioids stand atop.

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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 is a synthetic opioid derivative possessing agonist-antagonist activity at opioid μ_2 -receptors and additional agonist activity at opioid -receptors. The analgesic efficacy of Butorphanol is comparable with that of Morphine, Mepiridine, and other opioids. However, the safety concerns with Butorphanol are much lower compared to other opioids, especially the addiction potential. The 14 years of safe and effective use of Butorphanol injection make Butorphanol the 'drug of choice' in a number of painful conditions. In recent years, nasal drug delivery systems emerged as a suitable alternative for the common route of intravenous and oral dosing. Nasal administration may offer advantages such as ease of administration, rapid onset and patient control. It bypasses gastrointestinal and hepatic presystemic elimination and is applicable in patients with nausea and vomiting. Nasal drug delivery provides prompt onset of action which is one of the primary objectives in treating acute pain episodes. Butorphanol nasal spray is formulated with the aim of better patient acceptance without compromising its therapeutic efficacy.

Aims and Objective

To compare the efficacy of i.v.butorphanol and transnasal butorphanol as an analgesic in Laparoscopic cholecystectomy. Advantages of nasal butorphanol. Effect of butorphanol on hemodynamic parameters.

MATERIAL AND METHODS

Study Type:Observational

Study Design: Prospective observational cohort Study

Study Setting: Department of Anesthesiology, BHU, Varanasi

Sample Size: 60 patients

The study was approved by the Ethical Committee of the hospital. A written informed consent was obtained from all the patients before the day of surgery. The patients were subjected to detailed clinical examination and routine investigations to exclude any systemic disorder.

Exclusion Criteria

- Hypersensitivity to the drug
- Elderly patients (age >60 yrs)
- Hepatic impairment
- Renal impairment
- Head injury and CNS depression

Study Procedure: All patients were premedicated with tab alprazolam 0.5mg and tab ranitidine 150mg orally in night before surgery and again two hour before surgery.

Patients were allotted to two random group:-

Group 1 received 2 mg butorphanoli.v. at the time of premedication

Group 2 received 2 mg butorphanol i.e. 2 puff of intranasal butorphanol

In the operation theatre monitors showing heart rate, ECG, NIBP, SpO₂ and EtCO₂ were connected and baseline readings were recorded. Patients in group 1 were given intravenous butorphanol 2 mg, glycopyrrolate 0.2mg and ondensetron 4mg before induction of anaesthesia. In group 2 patients were given 2 mg i.e. 2 puff of intranasal butorphanol 30 min before induction After preoxygenating the patients were induced with injection propofol 2mg/kg. Tracheal intubation was done after using vecuronium in dose of 100μ g/kg body weight. Anaesthesia was maintained with oxygen, N₂O, isoflurane and butorphanoli.v. 1 mg or intranasal butorphanol 1 puff given when VAS score more than 5.

Drugs used

Intervenous and Transnasal Butorphanol

Intranasal Butorphanol: Ringer lactate as i.v. fluid was administered at the rate of 15ml/kg 1st hour followed by 7.5ml/kg/hr till the end of surgery to all patients. The parameters to be observed would include heart rate, systolic, diastolic blood arterial blood pressure, visual analog score (VAS), ramsay sedation score. The heart rate, systolic, and diastolic blood pressure would be observed just before induction, after induction, at time of skin incision, 5, 10 min of pneumoperitoneum after release of pneumoperitoneum, after reversal from general anesthesia, 5min and finally 20 min after shifting to post anaesthesia care unit (PACU). Visual analog score, ramsay sedation score were measured at time of reversal and in the post anesthesia care unit. After surgery anaesthesia was reversed, neostigmine and glycopyrrolate in the dose of 50 µg/kg and 10µg/kg respectively were given for adequate neuromuscular recovery. Patients and the surgeon were blinded about the specific nature of drug being used in a particular patient (i.v.butorphanol and transnasalbutorphanol) but at the end of procedure it was explained.

All the patients were transferred to postanaesthesia care unit (PACU) after completion of satisfactory reversal. In the postoperative period any event of nausea and vomiting was recorded.

Parameters observed

- J Heart rate
- Blood pressure(systolic and diastolic)
- VAS score
- **)** Ramsay sedation score

Statistical Analysis: The mean and standard deviation (SD) of the parameters studied during observation period were calculated for two treatment groups and compared by student T test. Intra group comparison was done with Paired t-test. The critical value of 'P' indicating the probability of significant difference, was taken as <0.05 for comparisons.

Observation: Patients were assigned randomly to two groups of 30 patients each. Group I and Group II were maintained on i.v.butorphanol and transnasalbutorphanol respectively. The

minimum age in group I (i.v.butorphanol group) was 20 yr and maximum age was 62 yr. not significant (Table 1).

Table	1.	Age	distribution
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Group	Mean Age (Yrs)	t-value	p-value	
Group 1	36.07 <u>+</u> 5.529	0.131	0.896	
Group 2	36.27 <u>+</u> 6.068	0.131	0.890	

Hemodynamic Parameters

Table-2 Mean Heart Rate (Beats per minute) at various time intervals in both groups: Table 5 shows patient's heart rate at different time intervals in both the groups. The patient's heart rate was observed preinduction (HR_0), at the time of intubation (HR_1), at skin incision (HR_2), 5 min after pneumoperitoneum (HR_3), 10 min after pneumoperitoneum (HR_4), after release of pneumoperitoneum (HR_5), after reversal (HR_6), 5 min after shifted to PACU (HR_7) and 20 min after shifted to PACU (HR_8). In group I preinduction minimum and maximum heart rate was 63/min and 90 /min respectively with mean of 80.17 7.231. At the time of reversal minimum and maximum heart rate was 88/min and 94/min respectively with mean of 79.17 7.137. In group II preinduction minimum and maximum heart rate was 66/min and 95/min respectively with mean of 79.53 7.995. At the time of reversal minimum and maximum heart rate was 68/min and 90/min respectively with mean of 79.93 6.617.

In group I at the time of intubation, heart rate was seen with mean value of 75.83 6.364. In group II, rise in heart rate was seen after intubation and during reversal. In group I at the time of intubation heart rate was seen with mean 76.37 8.112. Paired t – test result shows t= - 0.283 and p = 0.778 which was statistically insignificant. At time of skin incision in group I mean heart rate 74.86 7.14, while in group II it is 75.20 7.54 with t = -0.177 and p = 0.86 which was statistically insignificant. After 5 minutes of pneumoperitoneum mean heart rate was 79.52 7.628, 79.63 6.886 respectively in group I and group II with t = -0.61 and p = 0.951 which was stastitically insignificant. After 10 minutes of pneumoperitoneum mean heart rate was 78.14 $\{7.275, 76.17\}$ 7.164 respectively in both group with t =1.052 and p = 0.297. Mean heart rate immediately after release of pneumoperitoneum in group-I 76.76 $\{7.477, \text{ in group II } 77.73 \}$ 5.901 with t = - 0.557and p = 0.58. At the time of reversal mean heart rate was 79.17 7.137. 79.93 6.697 respectively in both group with t = - 0.425 and p = 0.673 which was insignificant. First postoperative (5 min after shifting to PACU) mean heart rate value in both group I and group II respectively were 77.72 7.091 and 79.40 7.304 with t = -0.894 and p = 0.37.

Second postoperative (20 min after shifting to PACU) mean heart rate value respectively were 80.38 6.259 79.10 6.150 in grp 1 and grp 2 with t = 0.792 and p = 0.432. Both post operative mean heart rate value in grp 1 and grp 2 were compared and statistically significant differences not found. Systolic Blood Pressure (SBP) and diastolic blood pressure (DBP) was measured in preinduction (SBP_0), preintubation (SBP_1), at time of skin incision (SBP_2), 5 min after pneumoperitoneum (SBP_3), 10 min after pnemoperitoneum (SBP_4), after release of pneumoperitoneum (SBP_5), after reversal (SBP_6), 5min (SBP_7) and 20 min (SBP_8) after shifting to postoperative recovery room. Mean Systolic blood pressure in group I and group II at preinduction period respectively were of 127.86 12.406 and 127.87 10.204 with t = 0.999, p = - 0.002. Mean diastolic blood pressure in preinduction period were 76.76{7.434, 76.07 6.411 with t=0.383 and p = 0.703. Mean systolic blood pressure at preintubation in both group respectively were 121.77 11.380, 115.34 14.864 with t= -1.867 and p = 0.067. Mean diastolic blood pressure at preintubation were 71.66 $\{6.360, 72.43\}$ 5.740 with t = - 0.494 p = 0.623. Mean systolic blood pressure at skin incision were 123.79{11.047, 122.13{11.959 respectively with t= 0.553 and p = 0.582. Mean diastolic blood pressure at skin incision 78.83 7.649, 77.70 8.272 respectively with t = 0.543 and p = 0.589. Mean systolic blood pressure at after 5 min of pneumoperitoneum are 119.83{13.191, 126.13{9.413 and t = -2.119, p = 0.038. Mean diastolic blood pressure after 5 min of pneumoperitoneum in both group 78.55 8.441, 77.40 6.926 with t = 0.547, p = 0.568. Mean systolic blood pressure after 10 min of pneumoperitoneum124.38 9.159, 123.87 10.275 t = - 1.055, p = 0.296. Mean diastolic blood pressure after 10 min of pneumoperitoneum were 77.76 $\{8.223, 76.83\}$ 6.869 with t =0 .470, p = 0.640. Mean systolic blood pressure after release of pneumoperitoneum were 124.72 8.176, 127.17 10.296 t = -1.007 p = 0.318.

Mean diastolic blood pressure after pneumoperitoneum release in both were 76.59{7.481 77.47{6.329 with t = -0.489 p = 0 .627. Mean systolic blood pressure after reversal in both group were 126.66{8.558, 127.40{9.265 with t = -0.320 p = 0.750. Mean diastolic blood pressure after reversal in both group respectively 78.07{8.477, 78.17{5.718 with t = -0.052 p = 0.959. Mean systolic blood pressure 5 min after shifting to postoperative room in both group 1 and 2 125.93{8.652, 127.27{7.124 with t = -0.648, p = 0.519 respectively. Mean diastolic blood pressure 5 min after shifting to postoperative room 75.97{6.895, 77.93{7.786 respectively with t = -1.026, p = 0.309. Mean systolic blood pressure 20 min after shifting to postoperative room were 125.86{8.915, 128.10{7.327 with t = -1.055 p = 0.296.

Mean diastolic blood pressure after 20 min of postoperative shifting were 77.62 $\{6.466, 79.13\}$ 7.186 with t = -0.849, p =0 .399. Arterial oxygen saturation in both group 1 and 2 were observed at preinduction, at the time of intubation, at skin incision, 5 min after pneumoperitoneum, 10 min after pneumoperitoneum, after release of pneumoperitoneum, after reversal 5 min after shifted to PACU, 20 min after shifted to PACU and compared which showed statistically insignificant changes in both group. Ramsay mean sedation score immediately after reversal in two group were 2.03{0.325, 2.17 379 with t = -1.435 and p = 0.157 that is stastistically insignificant. Sedation score was evaluated in the post operative period, 5 min and 20 min after shifting to PACU. Mean sedation score were compared between both groups, no statistically significant difference noted. After reversal mean VAS score in both group mean are 4.62{0.622, 4.73{0.450 with t = -0.799 and p = 0.427 which was insignificant. Mean VAS score at 5 min of postoperative stay were 4.62{0.622, 4.73 { 0.45 with t = -0.799 and p= 0.427 Mean VAS score at 20 min of post operative stay in both group were 4.97{0.566, 5.23 0.679 with t = -1.643 p = 0.106.

Time interval	Group 1(n=30)	Group 2 (n=30)	t-value	p-value
HR_0	80.17{7.231	79.53{7.995	0.322	0.749
HR_1	75.83{6.364	76.37{8.122	-0.283	0.778
HR_2	74.86{7.140	75.20{7.540	-0.177	0.860
HR_3	79.52{7.628	79.63{6.886	-0.061	0.951
HR_4	78.14{7.225	76.17{7.164	1.052	0.297
HR_5	76.76{7.477	77.73{5.901	-0.557	0.580
HR_6	79.17{7.137	79.93{6.617	-0.425	0.673
HR_7	77.72{7.091	79.40{7.304	-0.894	0.375
HR_8	80.38 6.259	79.10{6.150	0.792	0.432

Table 2. Mean Heart Rate (Beats per minute) at various time intervals in both groups

Table 3. Mean Systolic Blood Pressure at various time interval in both group

Time interval	Group 1(n=30)	Group 2 (n=30)	t-value	p-value
SBP_0	127.86{12.406	127.87{10.204	-0.002	0.999
SBP_1	115.34{14.864	121.77{11.380	-1.867	0.067
SBP_2	123.79{11.047	122.13{11.959	0.553	0.582
SBP_3	119.83{13.191	126.13 9.413	-2.119	0.038
SBP_4	124.38{9.159	123.87{10.275	0.202	0.841
SBP_5	124.72{8.176	127.17{10.296	-1.007	0.318
SBP_6	126.66 8.558	127.40 9.265	-0.320	0.750
SBP_7	125.93 8.652	127.27 7.124	-0.648	0.519
SBP_8	125.86 8.915	128.10 7.327	-1.055	0.296

Table 4. Mean Diastolic Blood Pressure at various time interval in both groups

Time interval	Group 1(n=30)	Group 2 (n=30)	t-value	p-value
DBP_0	76.76{7.434	76.07 6.411	0.383	0.703
DBP_1	71.66 6.360	72.43{5.740	-0.494	0.623
DBP_2	78.83{7.649	77.70{8.272	0.543	0.589
DBP_3	78.55{8.441	77.40{6.926	0.574	0.568
DBP_4	77.76 8.223	76.83{6.869	0.470	0.640
DBP_5	76.59{7.481	77.47{6.329	-0.489	0.627
DBP_6	78.07{8.477	78.17{5.718	-0.052	0.959
DBP_7	75.97{6.895	77.93{7.786	-1.026	0.309
DBP_8	77.62 6.466	79.13{7.186	-0.849	0.399

Table 5. Mean value of SpO₂ (Arterial Oxygen Saturation) at various time interval in both group

Time interval	Group 1(n=30)	Group 2 (n=30)	t-value	p-value
SPO2_0	97.21{.902	97.23 .817	-0.118	0.906
SPO2_1	99.93{.258	100.00{.000	-1.465	0.148
SPO2_2	99.86{.581	100.00{.000	-1.301	0.199
SPO2_3	100.00{.000	100.00{.000		
SPO2_4	100.00{.000	100.00{.000		
SPO2_5	100.00{.000	100.00{.000		
SPO2_6	97.38 1.237	97.87 .507	-1.992	0.051
SPO2_7	96.93{.371	96.00{.000	13.735	0.000
SPO2_8	96.76{.689	97.00{.000	-1.918	0.060

Table 6. Comparison of Sedation score during postoperative period between two group

Time interval	Group 1(n=30)	Group 2 (n=30)	t-value	p-value
Sedation_6	2.03{.325	2.17{.379	-1.435	0.157
Sedation_7	2.00 {.000 ^a	2.00 {.000 ^a		
Sedation_8	$2.001.000^{a}$	2.00 {.000 ^a		

Table 7. Comparison of VAS score between the two group in post operative period

Time interval	Group 1(n=30)	Group 2 (n=30)	t-value	p-value
VAS_6	4.62 622	4.73{.450	-0.799	0.427
VAS_7	4.62 622	4.73{.450	-0.799	0.427
VAS_8	4.97{.566	5.23 .679	-1.643	0.106

DISCUSSION

Laparoscopic surgery (Mattioli et al., 2002) involves abrupt hemodynamic changes owing to CO₂ pneumoperitoneum (Menes, 2000), increased intra-abdominal pressure and positioning during this procedure. The study was performed in 60 patients of ASA physical status I and II divided randomly into two groups. Group I received injection butorphanol intravenous while group II received transnasal butorphanol spray. In both groups preinduction heart rate, systolic, diastolic arterial blood pressures were taken. Intraoperative and post operative heart rate, systolic and diastolic arterial blood pressure were compared at different time intervals. Postoperative sedation and visual analog score to quantify the pain relief was also included. In our study, in group I we used injection butorphanol 2mgi.v. Change in heart rate (Table 2) and blood pressure (systolic and diastolic) was noted from preinduction to 20 minutes after shifting to postoperative room. In our study group II we used transnasalbutorphanol 2mg i.e. 2 puffs sprayed. The nasal spray formulation is an effective analgesic for the relief of moderate to severe pain such as in upper abdominal laparoscopic, dental, maxillofacial, or other surgical pain. For the marketed therapeutic doses of 1 and 2 mg, clinical studies have indicated that the transnasal preparation is safe and effective with an analgesic efficacy similar injected butorphanol (Abboud et al., 1991; Diamond et al., 1991; Schwesinger et al., 1992). In our study, group 1 heart rate dropped from mean of 80.17 7.231 preinduction to mean heart rate of 75.83 6.364 at preintubation. In group 2 mean heart rate at preinduction phase was 79.53 7.995, it decreased to 76.37 8.122. In both group comparing heart rate showed drop but statistically insignificant p = 0.749. Blood pressure both systolic and diastolic were measured in both group and at preinduction, at preintubation. In group 1SBP mean was 127.86 12.406 at preinduction, SBP mean 115.34 14.864 at preintubation. In group 2 SBP were 127.87 10.204, 121.77 11.380 respectively. There was a statistically insignificant drop in blood pressure with p = 0.067. Likewise DBP showed insignificant change.

Hemodynamic parameter heart rate and blood pressure were measured at time of skin incision, after 5, 10 min of pneumoperitoneum and after release of pneumoperitoneum .In group 1 heart rate noted to be mean of 74.86 7.140, 79.52 7.628, 78.14 7.225 and 76.76 7.477 at time mentioned before. In group 2 mean heart rate recorded were 75.20{7.54079.63{6.886 76.17{7.164 77.73{5.901 at time respectively. Blood pressure recorded at skin incision 5, 10 min of peritoneal insufflations and after release of pneumoperitoneum in both group. In group 1 blood pressure mean were 123.79{11.047, 119.83{13.191, 124.38{9.159, 124.72 8.176 and in group 2 systolic blood pressure mean 122.13 11.959. 126.13 9.413, 123.87 10.275. were 127.17 10.296 respectively at time mentioned above. In both group 1 and 2 heart rate was stable intra operative but when both were compared p = 0.86, 0.93 suggesting no statistically significant changes in heart rate noticed in using butorphanol in intravenous and transnasal route. In group 1 SBP dropped at 5 min of pneumoperitoneum but otherwise stable till release of pneumoperitoneum. In group 2 blood pressure were stable till release of pneumoperitoneum. No statistically significant (p = 0.582, 0.318 0.8410.038) variation were noted between both group. Patient in both group were reversed from general

anaesthesia and shifted to post anesthesia care unit for monitoring of haemodynamic parameters and pain. Patients in both group monitored for heart rate and blood pressure changes, sedation and postoperative pain. Mean blood pressure at time reversal from general anesthesia, 5 min after shifting to PACU and finally after 20 min in group 1 126.66{8.558, 125.93{8.652, 125.86{8.915, and in group 2 were 127.40{9.265, 127.27{7.124, 128.10{7.327 respectively. No significant (p = 0.750, 0.519, 0.296) difference noted. Mean heart rate in both group respectively at time of reversal, 5 min and 20 min after shifting to PACU were 79.17{7.137, 77.72{7.091, 80.38{6.259 and 79.93{6.617, 79.40{7.304, 79.10{6.150 with p=0 .673,0.375,0.432 i.e. statistically insignificant.

Visual analog score used to assess the pain felt by patient immediately after recovering from general anesthesia up to 20 min of postoperative period. VAS score of mean in group 1 4.62{.622, 4.62{.622, 4.97{.566}} and in group 2 VAS were 4.73{.450, 4.73{.450, 5.23{.679. p =0.426, 0.187 suggest insignificant difference between two group. Ramsay sedation score to compare the sedation among two group suggest no significant difference. Hence in our study we can assume clinically that butorphanol in two different routes i.e. intravenous and transnasal has no significant difference in quality of analgesia, sedation and haemodynamicchanges. No trial study in this regard was conducted earlier. But patient population being very small so generalization of the results of this study over our population needs more validation.

Summary and conclusion

Randomized comparative study 60 ASA I and II physical status patients, 20 to 65 years of age were allocatted randomly in two groups (intra venous butorphanol and transnasalbutorphanol) of 30 patients each. The patients were planned for laparoscopic cholecystectomy under general anaesthesia. Patients with history of hypertension, ischemic valvular heart diseases. heart disease, diabetes, glaucomaHypersensitivity to the drug, Elderly patients (age >60 yrs), Hepatic impairment, Renal impairment Head injury and CNS depression were excluded from the study. In group I injection i.v.butorphanol 2 mg was given at the dose of 30the premedication. $40\mu g/kg$ In in group Π transnasalbutorphanol 2 mg i.e. 2 puffs was spray 20 min prior to induction. Preinduction heart rate, blood pressure was measured. Anaesthesia was induced and vitals at the time of induction were also noted.

After induction heart rate, mean arterial blood pressure was noted at time of skin incision, 5 and 10min of pneumoperitoneum, after release of pneumoperitoneum, after reversal from general anesthesia and finally 5 and 20 minutes after shifting to post anesthesia care unit. In conclusion, we found that in both group haemodynamic parameter like heart rate and blood pressure were stable in each group. All 60 patients were followed up in the post operative recovery room and haemodynamic parameter noted and VAS score assessed to compare the analgesic efficacy of different routes of butorphanol administration in these patients. Ramsay sedation score noted in both group of patients. The observations of our study suggest that butorphanol as such can be used but different route has no significant change in analgesic efficacy and sedation.

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