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Trans Nasal Butorphanol for Post Operative Analgesia in Lower Abdominal Laparoscopic Surgeries

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ABSTRACT
Background: *Postoperative pain is acute with complex physiological responses to tissue injury. Trans nasal Butorphanol has been found to provide better pain relief and also decreased incidence of postoperative complications.*
Aim: *This study was done to know onset, duration, quality of analgesia, cardio-respiratory effects and side effects of Transnasal butorphanol for the relief of postoperative pain in lower abdominal laparoscopic surgery*
Methods *A total of 60 patients of females, belonging to 20-60 yrs of age, ASA grade I and II admitted for lower abdominal laparoscopic surgeries were selected randomly for the study. Patients were divided into 2 groups as 30 each Group A- Butorphanol 1mg nasal spray, Group B- normal saline nasal spray was used as the study drugs for the relief of postoperative pain. Onset of analgesia, Duration of analgesia, Quality of analgesia, Level of consciousness, Cardio-respiratory effects, Side effects were recorded.*
Results *:In our study the mean time of onset of analgesia in Butorphanol group (group-A) was 11.3±2.25 (SD) min and the duration of action of analgesia was 4.86±1.02 (SD) hrs which are statistically significant, Quality of Analgesia (VAS) was good, with majority of the patients grading their pain relief as excellent. Sedation score was maximum at 30 mins after administration later there was gradual decrease in sedation score due decrease in analgesic action of Butorphanol. Incidence of side effects like nausea and vomiting were also negligible. No significant respiratory depression was seen in either group.*
Conclusion: *Transnasal Butorphanol spray is a safe and efficacious drug for post-operative analgesia. It provides a rapid, excellent but shorter duration of analgesia. It has mild sedation which is advantageous in the postoperative period.*
Key words: *Transnasal, Butorphanol, Laparoscopic Surgeries*

INTRODUCTION

Pain is defined as "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage"**.** Relief from pain is the most frequent indication for surgical intervention. The incidence of post operative pain varies with the individual patients, but is largely governed by the site and nature of operation. Pain after an operation is largely a result of direct injury caused to the tissues, but may be further aggravated by associated reflex muscle spasm or visceral distention. Its manifestation of autonomic,

psychological and behavioral responses results in unpleasant, unwanted sensory and emotional experience. It is of two characteristic types a dull steady pain at rest and a more severe stabbing pain associated with movement. Post-operative pain is a self limiting phenomenon, ***most intense during the first 24 hours and diminishes during the next 24 hours*.** Pain is minimal after 3-4 days following surgery. Post operative pain is often associated with increased incidence of other unpleasant symptoms like nausea, vomiting, sweating and can be a cause of post operative hemodynamic alterations.[1]

Effective pain control is essential for optimal care of surgical patients; especially in patients undergoing orthopedic surgeries as these patients suffer from considerable pain in the postoperative period. Despite advances in knowledge of patho-physiology of pain, pharmacology of analgesics and development of effective techniques for post-operative pain control, many patients continue to experience considerable discomfort. Management of post op pain has been done in two phases, one is preventive aspect and the other is the actual treatment of the pain. The preventive phase can play a significant role by preoperatively preparing the patient psychologically by explaining the surgical procedure and the probable intensity of pain. Pharmacological preparation by adequate premedication and by observance of accepted surgical principles and good anesthesia coupled with proper post operative care to minimize the amount of postoperative pain.[1,2]

The general methods of controlling post operative pain are being used.***1)Drug* treatment of post operative pain**: narcotics and non narcotic analgesics, sedatives and antispasmodics.2) ***Regional techniques***: Intercostal blocks, thoracic paravertebral block, Caudal block in children (sacra epidural), Continuous caudal block in adult, Continuous brachial plexus block, Continuous analgesia for abdomino thoracic wounds by infusion of local analgesic solution by epidural route[3,4].

Epidural blockade is becoming one of the most useful & versatile procedures of current day anesthetic practise Unique in that it can be placed at virtually any level of the spine, allowing more flexibility in its application**.** Is more versatile than spinal anaesthesia, as it can provide both anesthesia & analgesia, as well as treatment of chronic disease syndromes[5]**.** Epidural analgesia is a safe technique for post-operative pain relief and equivalent to traditional analgesic methods. Epidural narcotics have been extensively used for post-operative analgesia. However, disadvantage with use of traditional drugs like morphine is that many side effects such as nausea, vomiting, pruritis, urinary retention, drug dependence and delayed respiratory depression have been reported. They can not be used in elderly patients.

With discovery of newer opioids like butorphanol, tramadol and fentanyl, a new era in pain relief has commenced. Butorphanol, a synthetic morphian derivative is a mixed agonist and antagonist non-narcotic opioid analgesic[6]. The advantage with these newer drugs is that their potency is comparable to that of morphine, produce lesser respiratory depression, easily available, larger margin of safety and lesser incidence of nausea, vomiting, urinary retention, pruritis compared to morphine. Hence it is feasible that the present study will be conducted to assess the safety and efficacy of post-operative analgesia with trans nasal butorphanol in lower abdominal laparoscopic surgery.

MATERIALS AND METHODS

This study was carried out in the department of Anesthesiology, Government general Hospital, Siddhartha Medical College from June2013 to October 2014. Total number of 30 patients in each group with inclusion and exclusion criteria were selected for study, during a period of 18 months (time bound study). patients are divided into 2 groups as

Group A- Butorphanol 1mg nasal spray was used as the study drug ,

Group B- normal saline nasal spray was used as the study drug for the relief of postoperative pain

Patients were allocated randomly to each group.

Inclusion criteria:

- Patients undergoing lower abdominal laparoscopic surgeries in the age group of 20-60 years of female sex of ASA grade I and grade II.

Exclusion criteria:

- Patients with ASA grade III, IV and V
- Those with known hypersensitivity to opioids.
- Patients, physically dependent on opioids.
- Patients with local infection / inflammation of nose and para nasal sinuses
- Uncooperative patients
- Patients not willing for participation in the study

During preoperative visit patient's detailed history, general physical examination and systemic examination was carried out. Basic demographic characters like age, sex were recorded.

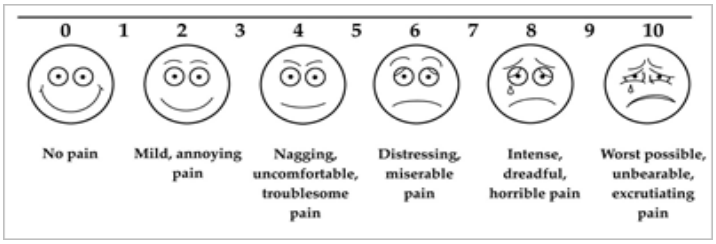
During the pre anaesthetic check up, linear visual analogue score LVAS was explained to all patients using a 10 centimeter scale. Written informed consent was taken from the patient. Preoperative vital data such as pulse rate, blood pressure...etc. noted; heart and lungs are examined .I.V. line established with 18 G I.V. cannula.

Premedicated with inj Glycopyrollate 0.2mg, inj.Ondansetron 4mg, inj.Tramadol 50mg used. Preoxygenation with 100% oxygen for3 – 5 min done. inj. Thiopentone sodium (5mg/kg) or inj. Propofol (2mg/kg) used. Intubation with suxamethonium (2mg/kg), OCET tube 7mm – 8mm ID is used. Connected to closed circuit N20:O2 4:3 lit/m connected to ventilator, tidal volume and ventilator rate set according to body weight. Inhalational agents (halothane or isoflurane) used according to necessity. Vecuronium bromide for longer duration surgeries and atracurium_besyllate for shorter duration surgeries.

No intra operative additional analgesics/anti emetics given. Reversal done with inj. Neostigmine +inj.Glyco used Patient extubated after full recovery. Patient shifted to post operative ward. In the post operative period when the patient complains of pain (moderate to severe) butorphanol nasal spray (1mg in each puff)given in group -A and placebo in group – B patients. The time of administration of drug and onset of analgesia, quality of analgesia duration of analgesia and complications are noted in each case. vital parameters such as pulse rate ,blood pressure respiratory rate were recorded at 0min,15min, 30 min,45min,60min, 2^{nd} 3^{rd} and 6^{th} hourly.

Duration of analgesia was calculated as time gap between 1^{st} nasal spray to subsequent demand by the patient for pain relief medication (Rescue analgesia), pain intensity was subsequently quantitiated 10cm linear visual analogue scale marked such that 0=no pain and 10=worst pain imaginable.

VAS scored as



Quality of Analgesia is scored as

1. Excellent analgesia, no pain or slight discomfort
2. good analgesia or patient comfortable but complains of $1/4^{th}$ of initial pain
3. good analgesia or patient comfortable but complains of ½ of initial pain
4. minimal analgesia or patient uncomfortable having $3/4^{th}$ of initial pain
5. No analgesia or complains of severe pain.

Patients were observed postoperatively and parameters like pulse, BP, respiratory rate and

duration of analgesia (the time when patient asked for rescue analgesia) were recorded as given in the proforma. After giving first dose of opioid (intra nasal butorphanol) following variables were assessed at 0 min, 15 min, ½ hour, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours and 24 hours in respect to, Onset of analgesia, Duration of analgesia, Quality of analgesia, Level of consciousness, Cardio-respiratory effects, Side effects(if any)

All the observations and particulars of each patient were recorded. Statistical software namely SPSS 18, were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables. results are presented on Mean ± SD, Significance is assessed at 5 % level of significance. Student t test (two tailed, independent) has been used to find the significance of duration of analgesia, onset of analgesia and VAS scores between two groups. P value is Strongly significant when it is P≤0.01

RESULTS

60 adult patients belonging to ASA grade I and II of female sex in age group between 20- 60 years, posted for elective lower laparoscopic surgery were selected for the study. They were randomly allocated to two groups with 30 patients in each group. This comparative clinical study was undertaken to study the efficacy based on onset of analgesia, duration of analgesia, haemodynamics, quality of analgesia and side- effects.

Table-1: Demographic details of the patients

Age in years	Group A	Group B
20-30	2	3
31-40	4	5
41-50	10	12
51-60	14	10
Height in feet		
4 – 4.5	1	0
4.6 – 5	7	6
5 – 5.5	22	24
Weight in kgs		
40-44	1	6
45-49	10	7
50-54	11	9
55-59	7	7
60-64	1	1

Table-2: Time of onset and duration of analgesia

Analgesia	Group A	Group B
Mean time of onset of analgesia(minutes)	11.3 ± 2.25	-
Mean Duration of analgesia (hrs)	4.86 ± 1.02	-

The mean time of onset of analgesia in group A was 11.3 ± 2.25 (S.D) minutes. 73.3% of patients in group A had onset of analgesia by 10 minutes and 26.7% of patients by 15minutes.Statistical analysis showed that onset of analgesia in group A was rapid and found statistically strongly significant with (p< 0.01).

Table-3: Comparison of pulse rate and respiratory rate in groups

Time	Mean	SD	Mean	SD
	Group A (Butorphanol)		**Group B (Placebo)**	
Pulse Rate				
0 Min	80.53	5.65	76.73	6.60
15min	79.36	5.79	76.6	5.37
30min	79.73	4.97	78.57	5.37
45min	78.37	3.77	81.93	5.58
1hr	78.1	3.72	82.93	5.35
2hrs	78.1	3.87	82.93	5.05
3hrs	78.1	3.3	83.33	4.6
4hrs	78.2	3.26	86.47	2.84
6hrs	80.3	6.17	86.27	1.23
Respiratory Rate				

0 Min	16.96	1.4	16.83	3.05
15min	16.8	1.00	17.87	1.02
30min	16.8	0.98	18.03	1.01
45min	16.8	1.07	18.33	0.94
1hr	16.9	1.02	17.83	0.68
2hrs	16.4	1.35	17.37	1.30
3hrs	16.8	0.92	17.57	0.49
4hrs	16.6	0.92	18.07	0.77
6hrs	16.6	2.2	18.13	0.95

The table shows that PR decreased after the administration of butorphanol up to 4hrs and later increased as the duration of analgesia was weaning off in study group. In control group (placebo group) there was increase in pulse rate as there was no pain relief.

There is little decrease in respiratory rate after administration of intra nasal butorphanol up to 3hours later there was little increase There was significant increase in respiratory rate after administration of placebo as there was no pain relief after the administration of placebo.

Table-4: Blood Pressure Distribution

Time	**Group A (Butorphanol)**		**Group B (Placebo)**	
	Systolic	**Diastolic**	**Systolic**	**Diastolic**
0 min	120	77.0	115	76
15min	120	75.3	115	76.73
30min	116	74.5	116.8	76
45min	115	74.3	116.6	77
1hr	114	75.7	116.8	77.2
2hrs	113	74.7	117	77.5
3hrs	112	74.7	118	77.9
4hrs	114	73.2	118	78
6hrs	114	76.1	120	80

The above table shows a gradual fall in SBP after the administration of study drug (Butorphanol)in group A upto 2-4 hrs followed by increase thereafter.

Diastolic BP decreased after administration of intra nasal butorphanol. There was increase in both systolic &diastolic BP after administration of placebo as there was no pain relief with placebo.

Table-5: Mean Values of Visual Analogue Scores of Two Drugs

Time	**Group A (Butorphanol)**		**Group B (Placebo)**	
	Mean	**SD**	**Mean**	**SD**
0 min	5.0	0	4.5	0.5
15min	1.1	0.3	5.0	0
30min	1.07	0.25	5.0	0
45min	1.13	0.5	5.9	0.3
1hr	1.1	0.4	5.8	0.37
2hrs	1.41	0.62	5.8	0.4
3hrs	2.3	0.74	6	0
4hrs	2.93	1.39	6.7	0.4
6hrs	5	0	6.7	0.45

The table shows that VAS scores in groupA (intra nasal butorphanol group) were lower (minimal to mild pain) for upto 3 hrs followed by gradual increase which is statistically significant when compareed to group B (Placebo group) which showed VAS scores increased continuosly upto 6

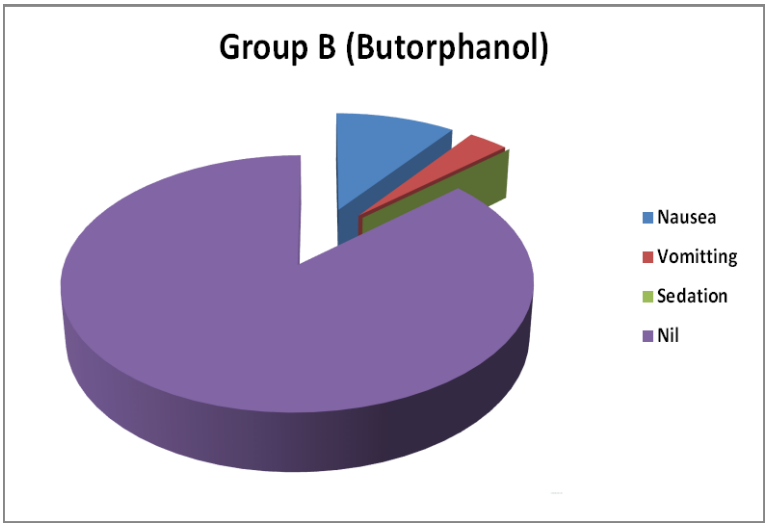
hrs.

Table-6: Mean Sedation Scores

Time	Group A (Butorphanol)		Group B (Placebo)	
	Mean	SD	Mean	SD
0 min	0	0	0	0
15min	0.9	0.3	0	0
30min	1.13	0.34	0	0
45min	0.46	0.49	0	0
1hr	0.5	0.5	0	0
2hrs	0.73	0.44	0	0
3hrs	0.53	0.49	0	0
4hrs	0.27	0.44	0	0
6hrs	0	0	0	0

sedation score increased after the administration of Butorphanol in study group(A). Sedation score was maximum at 30 mins after administration later there was gradual decrease in sedation score due decrease in analgesic action of Butorphanol. No sedation was observed in placebo group. Mild sedation was advantageous in early post operative period which was seen with Butorphanol.

Figure-1: Side Effects with Butorphanol



In our study majority of the side effects were nausea, vomiting and sedation.

Mild sedation is seen with the butorphanol group 16 (53%) .

DISCUSSION

Acute post-operative pain is a complex physiologic reaction to tissue injury. Pain is unpleasant sensory emotional experience associated with actual or potential tissue damage. There are two components of pain; physiological and pathological. Post operative pain is due to direct trauma to the tissue caused by surgery but may be aggravated by associated reflex muscle spasm or visceral distension. Pain being a subjective experience, it is difficult to convey or assess the severity. However in clinical practice two basic approaches in forms of subjective assessment by patients and objective assessment of parameters altered in presence of pain like cardiovascular changes and respiratory changes in response to pain are studied to judge the severity of pain.

Management of post operative pain still poses lot of challenges to anesthesiologists, in spite of advances in anesthesia and analgesia. Presence of pain indicates presence of some disease or damage in the body. Cutting, tearing, stretching and burning of tissues during surgery produces intra operative and post operative pain. If this surgical pain is not treated adequately, it may lead to derangement in various body functions. So treating pain is necessary to reduce the post operative morbidity and mortality.

Opioids are powerful, centrally acting agents which have peripheral effects also, so opioids have been administered for many years to allay anxiety and to reduce pain associated with surgery. Opioids exert this therapeutic effect by mimicking the action of endogenous opioid peptide at opioid receptors. In recent times role of non invasively administered opioids (Transnasal Butorphanol) for the post-operative pain promotes a new platform in this field as they have wider margin of safety and acceptability.[7]

Butorphanol is a synthetic morphine derivative introduced into Indian since 2002 is a mixed agonist and antagonist non-narcotic opioid analgesic. The analgesic potency of Butorphanol has been found to be greater than morphine and pethidine. Butorphanol unlike morphine, exhibits a ceiling effect on respiratory depression. Thus this study was conducted in an effort to assess efficacy and safety of newer drug butorphanol and compare it against Placebo.

In our study, a total of 60 patients belonging to age group 20-60 yrs were, divided randomly into two groups(n=30). There were no differences between two groups with regard to demographic profile. Mean age in group-A (receiving trans nasal butorphanol) was 28.6 and in group B (Placebo) was 23.4

In our study the mean time of onset of analgesia in study group-A was 11.33±2.24 (SD) min. The statistical analysis showed that the difference between the time of onset of analgesia in group-B and group-A is ($p<0.01$) which is statistically significant. Onset of action of tramadol in a study conducted by Pinky et.al [8] and others who used 100mg of epidural tramadol is 12±3.53 min which is comparable to our studies[9,10,11]. Whereas onset of analgesia was about 21±3.5 with use of 50 mg tramadol in another study conducted by Baraka et al. [12] A study by Mokhlesi [13] showed that onset of action with 4 mg butorphanol was 15 min and 6.9±3.6 in another study by Catherine O Hunt [14] in 1989 when, 2mg butorphanol was mixed with 0.25% bupivacaine.

With reference to above studies, butorphanol produced a more rapid onset of analgesia than tramadol in our present study. This rapidity of onset is attributable to high lipid solubility and high affinity of butorphanol for opioid receptors compared to that of tramadol. The duration of action of analgesia in Butorphanol group(A) was 4.86+1.02(SD) hours. In a study by Catherine O Hunt[14], duration of analgesia was 220±24.1 min after using 2mg epidural butorphanol combined with bupivacaine. In a comparative study of epidural morphine with epidural butorphanol by Palacios QT[15] median time of duration of analgesia was 3,2.5 and 4 hrs for butorphanol 1,2 and 4 mg respectively. The duration of analgesia in our study was comparable and was more than the above studies.

In our study, even though there is mild reduction in PR and BP with in butorphanol group, the cardiovascular and respiratory parameters were stable in this group. The fall may be due to adequate analgesia resulting in less sympathetic discharge and comfortable sleeping. Our study, Butorphanol group (group A) patients had lower VAS scores & moderate to excellent

Pain relief though for short duration, upto 3-4 hrs when compared to Placebo group (group B) patients who showed gradual increase in the severity of pain throughout the study period, and their demand for rescue analgesia was higher than Butorphanol group. Our study majority of the side effects were nausea, vomiting and sedation. Mild sedation is desirable in the post-operative period, which is seen with the butorphanol group 16 (53%)

CONCLUSION

Transnasal butorphanol (1mg) is a safe and efficacious drug for post-operative analgesia. Transnasal butorphanol provides a rapid, excellent analgesia when compared to Placebo which provides no pain relief. Intranasal butorphanol had side effects like nausea and vomiting but has sedation in milder degree which is an additional advantage in the post-operative period. Quality of analgesia in terms of patient satisfaction is also better with intra nasal butorphanol when compared to placebo

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