A Comparative Study of Post-Operative Analgesic Efficacy of Fentanyl, Butorphanol, Pethidine by Intranasal Route

Authors
Anita Pareek¹, Poonam Chand², Aditya³, Naresh Kumar Sharma⁴
¹Sr. Professor, ²Resident Doctor, ³Medical Student, ⁴Sr. Resident
Dept of Anaesthesiology, Sardar Patel Medical College, & A.G. of P.B.M Hospital, Bikaner

Abstract
Background: Pain is main post operative adverse outcome causing patient distress, prolonging hospital stay, and increasing the incidence of admissions after surgery. Study was done to assess and compare the post-operative analgesic efficacy of fentanyl, butorphanol, pethidine by intranasal route.

Methods: This study was conducted in the department of Anaesthesiology, Sardar Patel medical college and associated group of Hospitals Bikaner after taking permission from institutional research board. All eligible patients divided into 3 different groups: Fentanyl, Butorphanol & Pethidine administered intranasally for post-operative pain management.

Results: Onset of analgesia was less in group I (fentanyl) 7.6±1.16 than group II (butorphanol) 10.23 ± 1.52 and group III (pethidine) 13.23 ± 2.06. Duration of analgesia was more in group II (butorphanol) 280 ± 36.17 than group I (fentanyl) 188 ± 28.06 and group III (pethidine) 187 ± 28.33 and rescue analgesia used in group II (butorphanol) is less than other groups. Adverse effect like nausea, vomiting and bitter taste in group II (butorphanol) is less than other groups.

Conclusion: Intranasal instillation of butorphanol can certainly be recommended as a routine technique to improve postoperative analgesia.

Keywords: Butorphanol, Post-Operative Analgesia, Intranasal Administration, Side-Effects.

Introduction
Pain is defined as an “unpleasant physical and emotional experience due to tissue damage”. Pain is the most frequent cause of suffering and disability. The incidence of postoperative pain varies with the individual patients, but it largely governed by the site and nature of operation. Pain after an operation is largely a result of direct injury caused to the tissue, but may be further aggravated by muscle spasm or visceral distension. Its manifestation of autonomic, psychological and behavioural responses results in unpleasant, unwanted sensory and emotional experience. It is of two characteristics types a dull steady pain at rest and a more severe stabbing pain associated with movement. Post-operative pain has adverse outcomes causing patient distress, prolonging hospital stay and increasing the incidence of admissions after surgery. Patient control analgesia (PCA) is frequently employed as a method for the provision of postoperative analgesia. The main advantage of PCA is titration of the analgesic drug according to the patient’s individual requirements, thereby maximizing pain relief and minimizing the risk of opioid overdose with subsequent respiratory
depression. Intravenous patient-controlled analgesia (PCA) with an opioid is a widespread therapy for postoperative pain relief. Intravenous PCA has been shown to provide excellent pain relief and patient satisfaction. Disadvantages of intravenous PCA are the necessity of intravenous access and a PCA-pump that restricts the patients mobility. Intranasal PCA (PCINA) has been developed as an alternative delivery mode. There is evidence that PCINA with opioids is equivalent to intravenous PCA with respect to pain relief, patient satisfaction and side effects. Hence this study was planned to assess and compare the post-operative analgesic efficacy of fentanyl, butorphanol and pethidine via intranasal route to provide better analgesia, anxiolysis and any adverse effects.

Material and Method

Study Design: Hospital based prospective, double blinded, randomized, comparative study.

Study Area: The study conducted at A Block Operation Theatre Department of Anaesthesia, S.P. Medical College, Bikaner.

Study Period: The study conducted from Sept 2017 to Aug 2018 (one yr duration)

Duration of Data Collection: 6 months

Study Population: Patients age 18 to 45 years of either sex ASA grade I,II scheduled for lower abdominal surgery under spinal anaesthesia

Sampling Technique: Randomized sampling.

Statistical Test: Unpaired T-test, Anova test

Sample Size: All patients eligible for inclusion in study as per inclusion criteria and reporting within study duration were included in the study after obtaining informed written consent through randomized sampling. They were further divided into 3 groups in proportion of 1:1:1. Total 90 patients divided in three groups 30 in each group.

Inclusion Criteria
1. Patients aged between 18 to 45 years.
2. Patients weight between 50 to 75 kg.

Exclusion Criteria
1. Patients aged < 18 years and > 45 years.
2. History of clinically significant cardiovascular, pulmonary, renal, neurologic, metabolic disease.
3. Patients with a history of chronic analgesic drug usage >1 month.
4. Allergy to fentanyl, butorphanol, pethidine.

Method

This study was conducted in the department of Anaesthesiology, Sardar Patel medical college and associated group of Hospitals Bikaner after taking permission from institutional research board. All eligible patients, after dividing into 3 different groups: Fentanyl, Butorphanol & Pethidine administered intra-nasally for post-operative pain management, were interviewed about their demographic details, preoperative assessment by ASA grade I/II as well as through vital parameters assessment and Sebrasz test and post-operative assessment was done by measuring SBP, DBP, MAP, Pulse rate, SPO2 and VAS score at various time points like 15 minutes after intranasal instillation, then every 30 minutes thereafter. Any complication or side effects were recorded if occur.

Data Analysis

- Results were interpreted in terms of mean ± standard deviation.
- Student’s unpaired t – test for Quantitative data.
- Anova test for proportions in qualitative data
- Collected data were entered into excel sheet & analysed with help of SPSS version 21.0 software.

Observations and Results

Mean age, sex and weight in all three groups are comparable and p value is <0.05 which is statistically insignificant.
### Table No. 1 Statistical analysis of onset of time of drug (minutes)

<table>
<thead>
<tr>
<th></th>
<th>Group-I</th>
<th></th>
<th>Group-II</th>
<th></th>
<th>Group-III</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Onset of time (min.)</td>
<td>7.6</td>
<td>1.16</td>
<td>10.23</td>
<td>1.52</td>
<td>13.23</td>
<td>2.06</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Onset of time in group I (fentanyl) 7.6±1.16 is less than group II (butorphanol) 10.23± 1.52 and group III (pethidine) 13.23± 2.06 and p value (0.001) which is significant.

### Table No. 2 Statistical analysis of duration of post operative analgesia (minutes)

<table>
<thead>
<tr>
<th></th>
<th>Group-I</th>
<th></th>
<th>Group-II</th>
<th></th>
<th>Group-III</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Duration of analgesia (minutes)</td>
<td>188</td>
<td>28.06</td>
<td>280</td>
<td>36.17</td>
<td>187</td>
<td>28.33</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Duration of analgesia in group II (butorphanol) 188±28.06 and group III (pethidine) 187±28.33 280±36.17 is more than group I (fentanyl) and p value is 0.001 which is significant.

### Table No. 3 Rescue Analgesia Used

<table>
<thead>
<tr>
<th>No. of Rescue Analgesia Used in no. of Patients</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>19</td>
<td>30</td>
</tr>
</tbody>
</table>

Rescue analgesia used when VAS score>5, in group II (butorphanol) rescue analgesia used for only 19 patients in comparison to group I (fentanyl) 30 and group III (pethidine) 30.

### Table No. 4 Statistical analysis of VAS Score at different time intervals

<table>
<thead>
<tr>
<th>Time minutes</th>
<th>Group-I</th>
<th></th>
<th>Group-II</th>
<th></th>
<th>Group-III</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 15min.</td>
<td>0.60</td>
<td>0.62</td>
<td>1.23</td>
<td>0.77</td>
<td>2.01</td>
<td>0.61</td>
<td>0.001</td>
</tr>
<tr>
<td>T2 45min.</td>
<td>0.03</td>
<td>0.18</td>
<td>0.46</td>
<td>0.50</td>
<td>0.63</td>
<td>0.55</td>
<td>0.001</td>
</tr>
<tr>
<td>T3 75min.</td>
<td>0.03</td>
<td>0.18</td>
<td>0.10</td>
<td>0.30</td>
<td>0.26</td>
<td>0.52</td>
<td>0.043</td>
</tr>
<tr>
<td>T4 105min.</td>
<td>0.26</td>
<td>0.58</td>
<td>0.20</td>
<td>0.40</td>
<td>0.70</td>
<td>0.95</td>
<td>0.010</td>
</tr>
<tr>
<td>T5 135min.</td>
<td>1.10</td>
<td>1.56</td>
<td>0.20</td>
<td>0.40</td>
<td>1.66</td>
<td>1.47</td>
<td>0.001</td>
</tr>
<tr>
<td>T6 165min.</td>
<td>2.36</td>
<td>1.97</td>
<td>0.53</td>
<td>0.68</td>
<td>2.63</td>
<td>1.86</td>
<td>0.001</td>
</tr>
<tr>
<td>T7 195min.</td>
<td>2.46</td>
<td>2.87</td>
<td>1.30</td>
<td>1.20</td>
<td>3.30</td>
<td>1.70</td>
<td>0.001</td>
</tr>
<tr>
<td>T8 225min.</td>
<td>1.10</td>
<td>2.00</td>
<td>1.93</td>
<td>1.48</td>
<td>1.83</td>
<td>1.91</td>
<td>0.158</td>
</tr>
<tr>
<td>T9 255min.</td>
<td>0.13</td>
<td>0.34</td>
<td>2.70</td>
<td>1.70</td>
<td>0.60</td>
<td>0.77</td>
<td>0.001</td>
</tr>
<tr>
<td>T10 285min.</td>
<td>2.46</td>
<td>1.85</td>
<td>0.20</td>
<td>0.48</td>
<td>0.50</td>
<td>0.50</td>
<td>0.001</td>
</tr>
<tr>
<td>T11 315min.</td>
<td>0.30</td>
<td>0.65</td>
<td>1.96</td>
<td>2.37</td>
<td>0.26</td>
<td>0.44</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Above table show that mean VAS Score of group II (butorphanol) is less than group I (fentanyl) and group III (pethidine) except at time T7,T8,T10 which is due to due to rescue analgesia used in group I and group III.
Table No. 5 Statistical analysis of side effect of drugs

<table>
<thead>
<tr>
<th></th>
<th>Group-I</th>
<th>Percentage (%)</th>
<th>Group-II</th>
<th>Percentage (%)</th>
<th>Group-III</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>4</td>
<td>13.3</td>
<td>2</td>
<td>6.66</td>
<td>7</td>
<td>23.33</td>
</tr>
<tr>
<td>Bitter taste</td>
<td>1</td>
<td>3.3</td>
<td>0</td>
<td>-</td>
<td>7</td>
<td>23.33</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>16.66</td>
<td>2</td>
<td>6.66</td>
<td>14</td>
<td>46.66</td>
</tr>
</tbody>
</table>

Side effects in group II (butorphanol) is only nausea and vomiting in 2 patients only, while in group I (fentanyl) and group III (pethidine) has nausea, vomiting and bitter taste in 5 and 14 patients respectively.

Discussion
Post-operative pain continues to be inadequately managed leading to patient discomfort and an increased incidence of a multitude of complications. The objectives of this study were to assess postoperative pain scores, analgesia prescriptions and their implementation and patient satisfaction with their pain control.

Effective postoperative pain management continues to be a challenging clinical problem, as evidenced by several studies from the United States and Europe which have reported that postoperative pain management remains poor and that up to 80% of patients experience pain after surgery.

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 fentanyl, butorphanol and pethidine) for the post-operative pain promotes a new platform in this field as they have wider margin of safety and acceptability.

Anez SC et al. (2006)² reviewed the literature on intranasal administration of fentanyl, meperidine and butorphanol to treat acute pain. The adverse systemic effects are similar to those described for intravenous administration, the most common being drowsiness, nausea and vomiting. Local effects reported are a burning sensation and bad taste with meperidine only.

In our study the mean time of onset of analgesia in group I, group II and group III was 7.6±1.16, 10.23±1.52 and 13.23±2.06 (p 0.001) which is highly significant. According to present study group I (fentanyl) showing the shortest onset of time as compared to group II (butorphanol) and Group III (pethidine). The Group III has longest onset of time.

In support of our results Dale O et al. (2002)³ also revealed that mean onset of time of intranasal fentanyl, butorphanol, pethidine vary from 12 to 22 minutes. In favour to our study Ericprommer et al. (2011)⁴ found that onset of analgesia for intranasal fentanyl was 7.0 minutes. Mitra Jabalameli et al. (2016)⁵ study prove rapid absorption of intranasal fentanyl (therapeutic level within 2 min) and provide significant reduction in pain score by 5 min that is comparable with our results. H W Striebel et al. (1992)⁶ in his study concluded that pain relieving effect after intranasal fentanyl occurred nearly as early as after intravenous administration. A highly significant pain reduction was seen within 10 min.

The duration of analgesia of different drugs in present study group I was 188±28.06 group II was 280±36.17 and group III was 187±28.33 p value is 0.001(<0.05) which is highly significant. In our study it was found that group II (butorphanol) has longest duration of action as compared to group I (fentanyl) and group III (pethidine).

The result were in concordance with a study done by David foster et al. (2008)⁷ concluded that duration of effect was directly related to intranasal fentanyl dose that is 120 minutes (75mcg) to approximately 240 minutes (200 mcg) after a single dose. Eric Prommer et al. (2011)⁴ in his...
study found that there is no significant difference between intranasal and intravascular routes in duration of analgesia for fentanyl which is approximately 180 minutes. Abhimanyu et al. (2015) showed that the duration of analgesia of butorphanol is 4.86±1.02 hours that these results are having similarity with our study. Lin Yang et al. (2015) found that intranasal administration of butorphanol is superior to either intravenous administration of butorphanol or intranasal administration of fentanyl. This may be mainly due to the inhibition of the postoperative stress response, relatively good physiological function because of complete absorption after intranasal administration which produced high quality and duration of postoperative analgesia and lower incidence of POCD in intranasal butorphanol which is support to our study.

The visual analogue scale was used to measure the pain intensity in present study. The VAS score was found less in group II at all time interval to group I (fentanyl) and group III (pethidine) except at initial time at T0, T1, T2 group I (fentanyl) has less VAS score than group II (butorphanol). It is because due to less onset of time of intranasal group I (fentanyl). At the time interval T7, T8, T10 VAS score of group II (butorphanol) is more as remaining both group reason being the rescue analgesia given on demand in group I (fentanyl) and group III (pethidine).

In support to our study Abhimanu et al. (2015) revealed that VAS score in intranasal butorphanol group were lower (minimal to mild) for upto 3 hours followed by gradually increased.

In present study in group II (butorphanol) only in 19 patients required rescue analgesia while in other both group rescue analgesia was required in all 30 patients.

In present study the most common adverse effects are nausea and vomiting. The incidence of nausea and vomiting was found maximum in group III (pethidine) 5, minimum in group II (butorphanol) 2 and in group I (fentanyl) 4. The bitter taste was found in only in group III (pethidine) group in 7 patients.

Lin yang et al. (2015) study shows, the incidences of nausea and vomiting were significantly lower in intranasal butorphanol as compared to intranasal fentanyl. This may be related to the antagonism of butorphanol to the opioid receptor.

According to H W Striebel et al. (1995) the bitter taste and burning sensation in intranasal pethidine is due to running down the back of throat. However other intranasal administered opioids such as fentanyl and butorphanol do not irritate nasal and pharynal mucosa.

But Desajardins PJ et al. (2000) found that intranasal butorphanol has two severe adverse events drowsiness and dizziness. This might be because of the higher dose they used (2 mg dose) however we used 1mg.

**Conclusion**

This study shows that intranasal instillation of opioid provided effective post operative analgesia. Intranasal butorphanol provides longer duration of analgesia with significant reduction in consumption of rescue analgesic drugs. The conclusion of this study is that intranasal instillation of butorphanol can certainly by recommended as a routine technique to improve postoperative analgesia. However larger randomised controlled trial are required to evaluate efficacy and complication of intranasal butorphanol.

**References**


