

# Comparative Assessment of Fentanyl and Butorphanol as a Post Operative Analgesic in Patients after Spinal Anaesthesia

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Received: March 31, 2015; Accepted: June 06, 2015, Published: June 20, 2015

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## Abstract

**Introduction:** Postoperative pain is the pain felt by the patient following a surgery which could be elective or emergency. This study investigates the efficacy and tolerability of butorphanol and fentanyl with a view to identify the safe and effective postoperative analgesic among them.

**Methods:** 60 patients undergoing spinal anaesthesia were randomly allocated to two groups receiving butorphanol or fentanyl. Patients falling into the category of ASA I/II were chosen and the VAS score of each of them were taken at various time points.

**Results:** Comparison of the mean of the various parameters shows that the mean age of the patients enrolled in the study was 45.17±12.12 with 63.3% being males and 36.7% being females. The mean time taken for Butorphanol to reduce the pain was 10±4.91 min while that of fentanyl was 19±7min. The mean duration of action for butorphanol was 107±35.6 min and of fentanyl was 116±19.9 min. Patients on both the drugs also experienced various adverse effects like chest heaviness, drowsiness, pruritus, nausea and vomiting.

**Keywords:** Postoperative pain; Butorphanol; Fentanyl; Visual Analogue Scale (VAS)

## Introduction

“Greatest happiness mankind can gain is not from pleasure, but relief of pain”- John Milton. Pain relief is one of the main aims of postoperative care. Despite the horde of analgesics available, optimal therapy for affording post operative pain relief is still elusive. The healthcare systems afford relief of pain. Postoperative care includes effective relief from suffering, anxiety, restlessness and helplessness as well. Relief of pain would reduce the incidence and development of late complications of surgery including chest infections, cardiovascular, gastrointestinal and metabolic symptoms [1]. There are wide range of analgesics available, presently are listed (Table 1). This classification of analgesics is comprehensive and encloses all presently available

**Table 1:** Classification of analgesics.

OPIOID ANALGESICS	NSAIDS	NON-OPIOID NON-NSAID
<b>Endogenous opioids:</b> Endorphins, Enkephalins, Dynorphins, Endomorphins	Acetaminophen	Flupirtine Nefopam Ziconotide
Natural opium alkaloids: Phenanthrene derivatives: Morphine, Benzylisoquinoline derivative: Papaverine	Salicylates: Acetylated aspirin  Salicylate salts: Choline Magnesium	<b>STEROIDAL ANALGESICS:</b>  Flumetroxone
Synthetic opium derivative: Morphine derivatives: Hydromorphone Codeine derivatives: Buprenorphine Benzomorphans: Pentazocine Phenylpiperidines: Meperidine Miscellaneous: Dextromoramide tartrate Miscellaneous: Lefetamine Meptazinol Tilidine Tramadol Tapentadol	Propionic acid: Ibuprofen  Indolacetic acid: Indomethacin  Pyrrole acetic acid: Tolmetin  Anthranilic acid: Mefenamic acid  Phenylacetic acids: Diclofenac potassium  Enolic acid: Piroxicam  Naphthalenone: Nabumetone  COX-2 selective: Celecoxib  Miscellaneous: Dipyracetil  COX and LOX inhibitors: Licofelone	<b>MISCELLANEOUS</b>  Antidepressants: Amitryptiline, Fluoxetine  Anticonvulsants: Carbamazepine, Gabapentin  Alpha adrenergic agents: Clonidine  NMDA receptor antagonist: Ketamine, Memantine  Putative agents: Botulinum toxins, Thalidomide  5HT- agonist: Naratriptan, Eletriptan  Local anaesthetics: Lignocaine, Lopivacaine  Cholinergics: Neostigmine, Magnesium, Cannabinoids, Nabilone  Muscle relaxants: Carisoprodol, Methocarbamol

analgesics in proper order. The understanding of pain pathway would be helpful in manipulation, for pain relief. Postoperative pain is distressing and requires comprehensive care to achieve pain relief.

Opioids have been and continue to be, the choice for pain relief. Various methods used to tackle postoperative pain are intravenous infusions, brachial plexus injections, combined spinal epidural infusions and intravenous patient controlled analgesia [2].

Fentanyl is a synthetic opioid acting on the  $\mu$  ( $\mu$ ) receptors and is almost 100 times more potent than morphine [3]. Butorphanol has agonistic action on K ( $\kappa$ ) receptors and mixed agonist antagonist on  $\mu$  ( $\mu$ ) receptors. The analgesic effect of Butorphanol is three times more potent than morphine.

Opioids have a wide spectrum of actions and effects. This study investigates the efficacy and tolerability of the two drugs, with a view to identify the safe and effective postoperative analgesic.

The aim of the study was to compare post operative pain relief with the two drugs Butorphanol and Fentanyl. The objectives revolved around noting the efficacy and adverse reactions of the two agents under constitution, despite using their equianalgesic doses.

### Patients and Methods

The study was conducted at the post operative ward of Father Muller Medical College Hospital, Mangalore and the study period was from August 2009-July 2011.

### Design

Randomized, prospective double blind study.

### Inclusion criteria

Adult patients of either sex of ASA I OR II, falling between the age groups of 20-65 years presenting for surgery under spinal anaesthesia were included after obtaining a written informed consent.

### Exclusion criteria

- Patients with history of asthma
- H/o cardiac or hepatic disorders
- Taking centrally acting drugs like antidepressants
- Diminished mental competence, deafness, visual disturbances which would prevent them to comprehend the Visual analogue scale (VAS)
- Pregnant or lactating mothers

### Details of the study

Visual analogue scores was regularly evaluated and a score >3 was considered significant enough to warrant treatment with one or the other randomised blinded drug, by intravenous route.

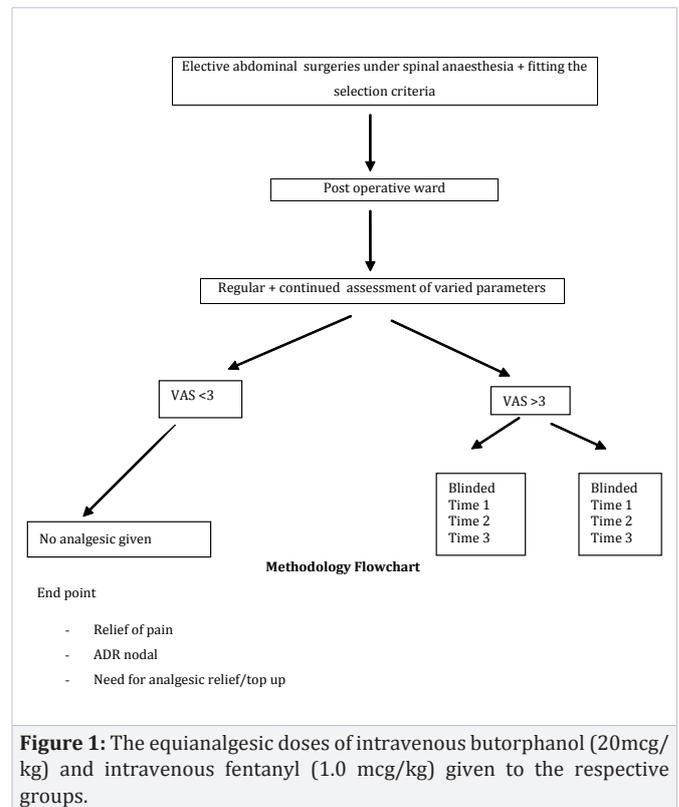
All patients were given 0.02 mg/kg midazolam, on arrival to

the operation theatre. In the operation theatre base line heart rate, blood pressure, SpO<sub>2</sub> were recorded before anaesthesia and repeated at intervals of 5 minutes for the remainder of the study.

At the end of the surgery, the vital signs and events noted and sent to in the postoperative ward. The VAS was used to document the severity of the pain.

The time at which the patient's complaints of pain with a significant VAS score of more than 3 was recorded as time 1, and the blinded drug was administered. The time 1 was recorded as time which the patient experienced relief of pain and the VAS score was again noted. The time when the patient again complained of pain was recorded time as 2 and the next dose of the blinded drug was administered.

The study drug was given when the score of 3 or more was recorded, the patient was randomly allocated to the study groups and relevant analgesics were administered intravenously. The equianalgesic doses of intravenous butorphanol (20mcg/kg) and intravenous fentanyl (1.0 mcg/kg) given to the respective groups are mentioned in Figure 1. The volume of the study drug and the capacity of the loading syringe were identical in both the groups. After intravenous administration, the onset and duration of the analgesia were noted. The observer, patient and the staff nurse were unaware of the drug being given. The VAS, Sedation score (Ramsay sedation scale), SpO<sub>2</sub>, respiratory rate, heart rate SBP and DBP were monitored at intervals of 1, 5, 15, 30, 60, 120 minutes and so on till the patient had a VAS score equal to or more than 3.



Before analysis, the blind was removed to interpret results from both groups.

## Results

### Age distribution

The mean age of the patients enrolled was  $45.17 \pm 12.12$  with a mean of  $44.20 \pm 11.53$  and  $46.13 \pm 12.80$  in butorphanol and fentanyl groups respectively.

### Sex distribution

Out of total 60 patients, 63.3% of them were males and 36.7% of them were females.

### Time of onset and duration of action

A mean time of around 10 minutes  $\pm 4.91$  was taken for butorphanol to help reduce the pain (onset of action Time 1 - Time 2 ) while compared to fentanyl which took a mean time of 19 minutes  $\pm 7$ . On the other hand the mean duration of action (Time 1 - Time 3) in butorphanol was 107 minutes  $\pm 35.6$  while that of fentanyl was  $116 \pm 19.9$  minutes.

### Adverse effects

Of the total 60 patients, 55% of them didn't experience any adverse effects. 21.7% complained of insufficient pain control, with a high significance in butorphanol when compared to fentanyl. The adverse effects included chest heaviness (1.7%), drowsiness (8.3%), Pruritus (13.3%), Nausea and vomiting (8.3%) and shivering (8.3%).

### Accessory use of drugs

Various accessory drugs were used to treat the adverse effects caused by fentanyl and butorphanol. Out of 60 patients, 21.7% were given other analgesics to bring down the pain, 6.7% were given anti-emetics for nausea and vomiting and 13.3 % were given antihistamines.

## Discussion

A pleasant postoperative period plays a vital role in the surgical outcome [4]. Our study tried to determine the comparative efficacy of both these drugs to produce postoperative analgesia. The study recruited 60 patients and divided them randomly into 2 separate groups to receive fentanyl and butorphanol respectively.

Our study showed a sex ratio of 63.3 % males and 36.7% females with a mean age of  $44.2 \pm 11.53$  in the case of butorphanol and  $46.13 \pm 12.80$  in the case of fentanyl. A study conducted by Frederic et al. [5] showed that women experienced more pain and hence required a higher dose of morphine when compared to men in postoperative period (Figure 2 and 3).

Butorphanol showed a rapid onset of analgesic effect (mean=10.00 min) when compared to that of fentanyl (mean=19.00 min) which was highly significant at a degree of freedom of 2.58. However the duration of analgesic effect with butorphanol (mean=107.50 min) and fentanyl (mean=116.00 min) was comparable but the difference doesn't hold any

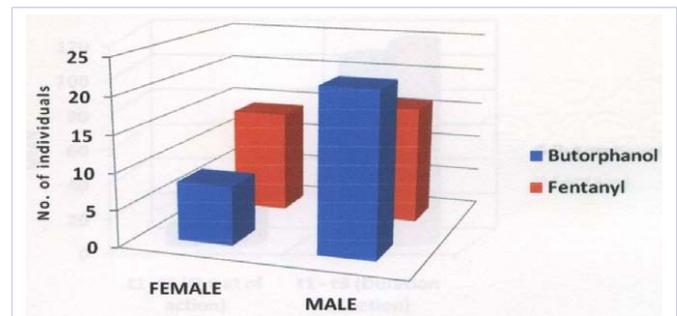


Figure 2: Demographic details: sex ratio of sample.

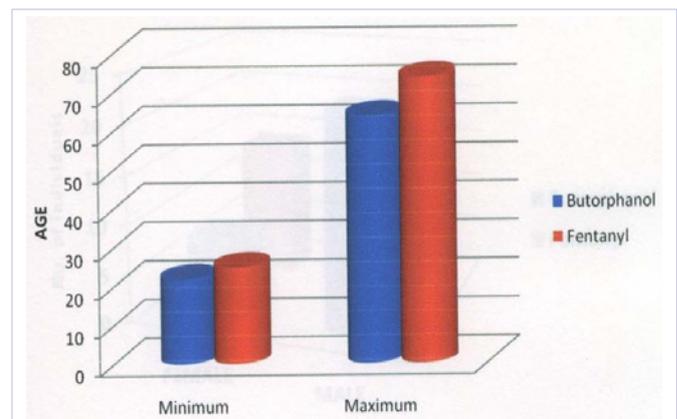


Figure 3: Demographic: Age Distribution.

statistical significance. A study done by Thakore et al. [4] showed that there was an increased demand of fentanyl due to its shorter duration of action when compared to butorphanol [6]. However this change could be due to the patient anaesthetics administered in this study (Figure 4 and 5).

The VAS score for butorphanol was lower at time 2 as opposed to fentanyl at the same time point. It was also noted that butorphanol had a relatively lower VAS score at time 3 as opposed to fentanyl. This indicates that butorphanol is capable of reducing the pain better than fentanyl as similar results were seen by Thakore et al. [4] Furthermore in our study we also observed that there were around 36.7% of the patients in the butorphanol group needed a rescue analgesic when compared to fentanyl which was 6.7% in contrast to the results obtained by Thakore et al. [5] (Figure 6 and Table 2(a,b,c)).

Adverse effects were observed in both the groups. Pruritus (16.7%) was the main complaint in fentanyl group whereas excessive shivering (16.7%) was the major adverse effect seen in butorphanol group in contrast to fentanyl group in which none experienced shivering. Apart from pruritus patients who received fentanyl also complained of chest heaviness (3.3%), drowsiness (13.3%), nausea and vomiting (10.0%). Other adverse effects among the butorphanol group included drowsiness (3.3%), itching (10.0%), nausea and vomiting (6.7%) (Table 2).

A study done by Scott et al. [7] showed that patients on epidural fentanyl with bupivacaine showed that the most

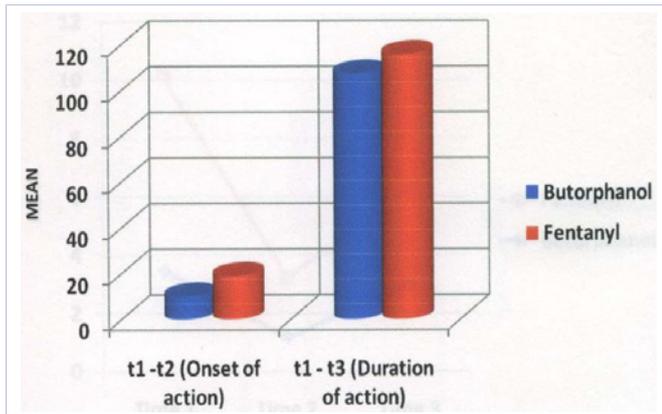


Figure 4: Onset and duration of analgesic action.

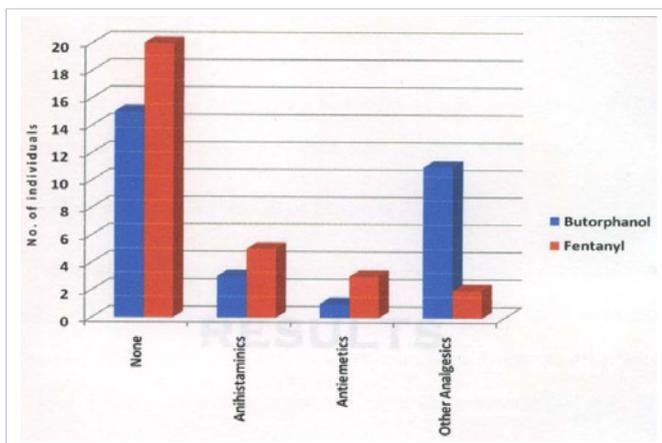


Figure 5: Accessory drugs used.

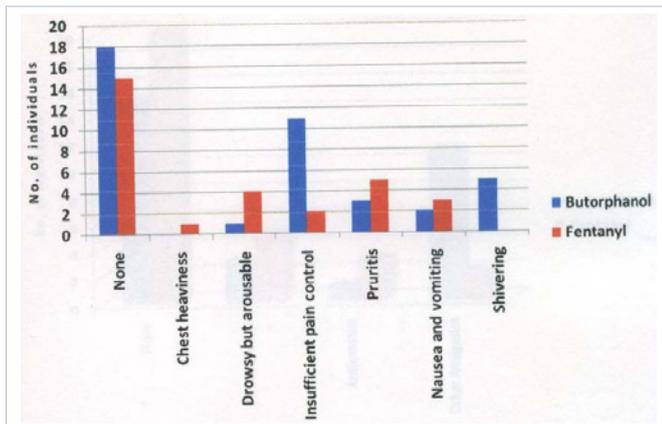


Figure 6: Occurrence of adverse effects among study groups.

common side effect was pruritus occurring in 10.3% of the cases followed by sedation (7.4%), hypotension (6.6%), nausea (4.8%), inflammation at the site (3.8%) and paralysis (3.0%).

Claxton et al. [8] conducted further study on postoperative pain relief over the fentanyl and found that the incidence of nausea and vomiting after discharge was higher in morphine than in fentanyl group. A similar study done by Wajima et al. [9]

which compared the effect of I.V butorphanol against brachial plexus administration showed the same adverse effects like nausea, vomiting and slight drowsiness and they too, were not significant.

In our study, the equi-analgesic activity of both butorphanol and fentanyl, although similar, butorphanol has an edge over fentanyl due to its favourable safety profile. Conclusions from other studies also indicate that butorphanol and fentanyl have similar efficacy profile for postoperative analgesia. Infact, Butorphanol has remarkable analgesic affect and other effects like anti-stressor, sedative and anti-shivering effect [10]. Postoperative pain gives rise to varied physiological and biological phenomena. Minimizing postoperative pain leads to, earlier mobilization and discharge from hospital, thus aiding recovery. Most of the opioid receptor agonists could bring about required postoperative pain. A rapid and effective analgesic is sought for postoperative pain. Opioids are the choice for severe pain but limited by the plentiful adverse effects.

The comparison of effect of fentanyl and butorphanol would bring out better analgesics for postoperative care.

Butorphanol is a synthetic lipid soluble opioid agonist with minimal adverse effects. The duration and quality of analgesia was matched with that of fentanyl.

Respiratory depression was not seen with either of the comparator drugs. Some studies were noted with epidural Butorphanol, a reduced carbon dioxide response curve. Various neuroaxial regional techniques e.g. epidural route is commonly employed for postoperative analgesia [11].

Fentanyl is highly lipophilic and rapidly diffuses with least tendency for respiratory depression with adverse effects due to systemic rather than spinal receptor binding [12].

The concomitant adverse effects of nausea, pruritus, shivering, vomiting and respiratory complications were recorded postoperatively upon questioning the patient; but their frequency was reduced.

The limitations of our study included small sample size and inclusion of only spinal anaesthesia cases. It would be interesting to note gender variations. The type of surgery could have a bearing on the postoperative pain which has not been considered in our study.

## Recommendations

Butorphanol and fentanyl could be advocated for regular postoperative analgesia due to its equianalgesic and minimal adverse effects. A study that incorporates more patients with various types of anaesthesia, considering various surgeries would be more conclusive. A pharmacogenomic evaluation could be undertaken.

## Conclusion

The assessment of butorphanol and fentanyl as a postoperative analgesic in abdominal surgeries under spinal anaesthesia, was investigated. The interesting chemical and receptor activity

Table 2a: ANOVA Test.

Drug	Time	n	Min	Max	Mean	Std. deviation	Median	ANOVA F Value	df	p value
b	Time 1	30	0	0	0.00	0.000	0.00	250.751	2.58	.0000 HS
	Time 2	30	5	30	10.00	4.913	10.00			
	Time 3	30	30	180	107.50	35.641	120.00			
f	Time 1	30	0	0	0.00	0.000	0.00	873.989	2.58	.0000 HS
	Time 2	30	5	35	19.00	6.998	20.00			
	Time 3	30	50	165	116.00	19.888	110.00			

Table 2b: Pair wise comparison: Bonferroni.

Drug	(I) Factor 1	(J) Factor 2	Mean Difference (I-J)	Std. Error	p value	Level of significance
b	Time 1	Time 2	-10.000	0.897	.000	HS
		Time 3	-107.500	6.507	.000	HS
	Time 2	Time 3	-97.500	6.423	.000	HS
f	Time 1	Time 2	-19.000	1.278	.000	HS
		Time 3	-116.000	3.631	.000	HS
	Time 2	Time 3	-97.000	3.429	.000	HS

Table 2c: Time of onset and duration of action.

Time	Drug	n	Min	Max	Mean	St. Deviation	Median	Mann Whitney Test Z value	p value
Change 1-2 <sup>nd</sup>	b	30	-30	-5	-10.00	4.913	-10.00	4.88	.0000 HS
	f	30	-35	-5	-19.00	6.998	-20.00		
Change 1-3 <sup>rd</sup>	b	30	-180	-30	-107.50	35.641	-120.00	1.15	.0249 NS
	f	30	-165	-50	-116.00	19.888	-110.00		
Change 2 - 3 <sup>rd</sup>	b	30	-170	-20	-97.50	35.178	-110.00	1.08	.0279 NS
	f	30	-135	-30	-97.00	18.782	-90.00		

dissimilarities brought these drugs under the scanner.

It was a randomized double blinded prospective, study. The observations noted were for the equianalgesic doses for butorphanol and fentanyl. Belying the lesser frequency of adverse effects with butorphanol, tops with fentanyl following closely.

Documentary evidence along with the outcomes of our study shows minor adverse effects and good analgesic activity with butorphanol and fentanyl. Overall, on comparison of the equianalgesic doses for butorphanol and fentanyl it show similar post operative analgesic effect and propensity for ADR.

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