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RESEARCH ARTICLE

A randomized clinical study comparing the analgesic efficacy of intra venous patient- controlled analgesia of morphine with fentanyl in post-operative pain management of major surgery patients

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ABSTRACT

Background: Post-operative pain is a protective but an unwanted effect which is to be treated for the better outcome of surgery. **Aims and Objectives:** The aim of this study is to compare the safety and analgesic efficacy of intravenous patient-controlled analgesia (IV PCA) using morphine and fentanyl for post-operative pain management in major surgery patients. **Materials and Methods:** The randomized clinical study initiated after the ethics committee approval and informed consenting. A total of 60 patients belonging to the American Society of Anesthesiology Grade - I, II, and III physical status, scheduled for major abdominal, oncological surgeries under general anesthesia were randomly allocated to two groups. Group M received IV PCA with morphine (basal continuous infusion 0.02 mg/kg/h, bolus dose of 0.02 mg/kg, and lockout period of 20 min), and the Group F received IV PCA with fentanyl (basal continuous infusion 0.5 μg/kg/h, bolus dose of 0.5 μg/kg, and lockout period of 20 min). Fentanyl dosage was converted into morphine equivalents. The outcomes such as visual analog scale (VAS), sedation score, hemodynamic parameters, and adverse effects were compared between groups and analyzed statistically. **Results:** Morphine provides better analgesia than fentanyl as indicated by lower VAS scores (score = 3) at the end of 24-72 h. Mean cumulative analgesic consumption was higher in fentanyl group (436.3 ± 330.2 mg) compared with morphine group (123.9 ± 28.2 mg) by 72 h. Regarding the hourly consumption, Group M consumed less drug than fentanyl group was statistically significant (P = 0.05). **Conclusion:** Morphine provides more effective post-operative analgesia than fentanyl administered through IV PCA. The PCA allows patients to balance between administration of analgesics and adverse events by self-adjusting the dose of analgesic used.

KEY WORDS: Intravenous Patient-controlled Analgesia; Fentanyl; Morphine; Post-operative Analgesia; Adverse Drug Reactions

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INTRODUCTION

Effective post-operative pain management following surgeries is a major concern for the both surgeons and anesthetists.[1] The technique used for post-operative analgesia should confer certain advantages over the other methods such as better pain relief, decreased

consumption of analgesics, better hemodynamics, and fewer adverse effects, allow early mobilization and high patient satisfaction.[2] Pain is an unpleasant sensory and emotional experience, and it is difficult to measure. It is a consequence of altered neuronal activity within the nociceptive system, consisting of peripheral afferents, spinal cord, brain stem, thalamus, and cortex. Therefore, enhanced neuronal activity in the nociceptive system can be taken as a measure of pain.[3] Pain is relieved with the usage of analgesic. Routes of analgesics administration include oral, transepithelial, parenteral, intramuscular, rectal, intravenous patient-controlled analgesia (IV PCA), intrathecal epidural, combined spinal epidural, and multimodal therapies.[4]

Individuals differ in their pain relief requirements. The inability to predict accurately the individual analgesic requirements suggested that a self-administration system may be the most efficient means of achieving analgesic effects. IV PCA is an interactive method of drug administration, in which a specific amount of medication (bolus dose) is delivered directly into patient's vein on pressing a button of the device. Furthermore, patient is in a position to maintain a satisfactory balance between pain relief and adverse effects and judges the effectiveness of the agents.[5] IV PCA boluses with lockout intervals have an advantage in maintaining serum drug levels within the analgesic range and further attenuate fluctuation in plasma level.[6] Morphine is commonly considered to be the archetypal opioid analgesic and the agent to which all other painkillers are compared. It is a potent hydrophilic, selective for μ opioid agonist, with slow onset of action, longer duration of action, less pulmonary first pass effect, less unionized form, and less plasma proteins bound.[7,8] Fentanyl is a potent lipophilic opioid agonist, but 100 times more potent than morphine, with rapid onset of action, shorter duration of action, undergoes significant pulmonary first pass effect, highly bound to plasma protein, larger volume of distribution, longer elimination halftime, longer context sensitivity halftime, and effect site- equilibrium time. It produces less histamine than morphine. It acts primarily as μ opioid receptor agonist.[9]

Inspite of its proven efficacy of morphine in pain management, the greatest limiting factor in its routine use is adverse effects such as respiratory depression, addiction, dependence, tolerance, nausea, vomiting, sedation, purities, and urinary retention. Few studies have been conducted to compare and assess the efficacy and safety of these opioid analgesics as IV PCA. The present study was conducted to (1) compare the clinical safety and efficacy of morphine and fentanyl administered by IV PCA for post-operative pain management in major surgeries and (2) compare the occurrence of adverse drug reactions (ADRs) in both the groups.

MATERIALS AND METHODS

Study Design

The study was randomized double-blinded clinical study, in which patients either received morphine for post-operative analgesia using IV PCA disposable infusion device (Group M) or receive fentanyl IV PCA (Group F). The simple randomization technique was used. This was double-blinded using opaque sealed envelope; both patients and the anesthesiologists/nurses managing post-operative pain were blinded to knowledge of the group to which they belonged.

Participants

This study was conducted in the Department of Anesthesia and Pain Management Center at Manipal Hospital, Bengaluru, during 2008-2009. The study was initiated after obtaining Hospital Ethics Committee approval. The informed consent was obtained from all patients before the enrolment. This study was conducted according to the declaration of Helsinki and the guidelines for good clinical practice.

Pre-anesthetic examination (PAE) included history, clinical examination, and systemic examination was done. Investigations such as hemoglobin, total counts, differential count, erythrocyte sedimentation rate, urine routine, random blood sugar, electrocardiogram (ECG), chest X-ray, serum aminotranferases, bilirubin, serum creatinine, and blood urea were done before PAE.

Inclusion Criteria

The study was designed to include 60 patients between 18 and 60 years of age of either gender with physical status of an American Society of Anesthesiology Grade I, II, and III physical status, scheduled for different types of major abdominal, faciomaxillary, orthopedic, oncological surgeries under general anesthesia.

Exclusion Criteria

Patients with a history of allergy and contraindication to the study drugs (morphine/fentanyl), refusal for usage of PCA as a pain management method, history of hepatic, cardiopulmonary or renal disease, hemodynamic instability, head injury patients, history of any chronic pain or drug history of analgesics, administration of opioid in the past 4 h, history of substance abuse, and psychiatric disorder were excluded. The patients refuse to consent, pregnant or lactating woman, and pediatric and geriatric age group were excluded from the study.

Interventions

After the surgery, the patients were shifted to recovery room and monitored continuously using non-invasive blood

pressure (BP), pulse oximeter, ECG, and respiratory rate (RR). After recovery (as judged by the ability to open the eyes, grip a finger, and breathe deeply on request) when patients complaints of pain, IV PCA drugs were started using PCA device through a dedicated IV line.

The following test drugs were given to the post-operative patients as per the randomization list.

- Group M: Patients receive IV PCA with morphine (basal continuous infusion 0.02 mg/kg/h, bolus dose of 0.02 mg/kg, and lockout period of 20 min).
- Group F: PCA with fentanyl (basal continuous infusion 0.5 mcg/kg/h, bolus dose of 0.5 mcg/kg, and lockout period of 20 min). The fentanyl dosage was converted into morphine equivalents (MEs). We considered 1 mg of morphine is equal to 0.01 mg of fentanyl.

All patients were instructed and educated about the use of patient-controlled analgesia device (GRASEBY 3300; GRASEBY Medical Watford, UK). The dosages and time intervals are preset into a microprocessor-controlled infusion pump. When the patient experiences pain, a button is pressed by the patient, and a dose of morphine is administered intravenously. If the patient should depress the button before the preset time interval (lockout interval) has elapsed, no extra drug is administered. PCA pumps allow a maximum dosage over a defined period to be preset to avoid patient overdosage.

Outcomes

The pain intensity, sedation scores, cumulative analgesic consumptions, hourly analgesic consumption, and ADRs were measured.

The cumulative analgesic consumption recorded at different intervals, namely,1, 2, 6, 12, 24, 36, 48, and 72 h. Furthermore, hourly analgesic consumption for each interval was calculated by dividing the analgesic consumed during that time interval with the duration of the time interval in hours. The study was terminated at the end of 72 h or on patient request to discontinue the IV PCA. Supplementary drugs used during the entire study period were noted at the end of the study.

Pain Assessment

The pain intensity was assessed by visual analog scale (VAS) ranging from 0 cm-no pain to 10 cm-possible worst pain. The patients were instructed to point out the intensity of pain on the scale (0-10).[10]

Sedation level assessment by Wilson et al. 1990[11] as: I - awake alert, II - awake and drowsy, III - eyes closed but arousable to verbal commands, IV - eyes closed but arousable to mild physical stimulation, and V - eyes closed and unarousable.

The incidence of occurrence of ADRs was noted in both the study groups. For example, nausea, vomiting, pruritus, desaturation or hypoxemia (SpO_2 <90%), respiratory depression (RR <10 beats/min), hypotension (decrease in systolic BP more than 20% of the baseline value), hypertension, bradycardia (pulse rate <60 beats/min), constipation, and urinary retention were observed.

Statistical Analysis

Statistical analyses were carried out on the data using software (SPSS 21 version). Analysis of normality was performed using the Kolmogorov-Smirnov test. Parametric data were presented as frequency, percentage occurrence, and mean ± standard deviation. The demographic data were analyzed using either Student's *t*-test or Chi-square test. VAS scores were analyzed with analysis of variance using general linear model for repeated measures. The complications were analyzed using Chi-square test or Fischer's exact test. $P = 0.05$ or less was considered for statistically significant.

RESULTS

A total number of 73 patients were screened for the eligibility, and 60 were enrolled. Excluded 13 patients (hemodynamic instability = 04, prior opiod usage = 03, contraindications to study drugs = 03, refused consent = 03) and 60 patients were randomized into the two groups (morphine and fentanyl). Baseline demographic profile of the patients is summarized in Table 1. Both the groups are comparable with respect to age, gender distribution, hemodynamic parameters, VAS, and sedation scores. The post-operative visual analog score throughout 72 h is shown in Figure 1. The patients in morphine group had better pain relief (lower VAS) throughout post-operative period than patients in fentanyl group ($P < 0.05$).

The cumulative analgesic consumption (ME/milligrams) is shown in Figure 2. Fentanyl is given as ME. Post-operative

Table 1: Baseline demographic profile of the patients

Parameters	Mean±SD		
	Group M (morphine)	Group F (fentanyl)	*P*
Age (years)	47.7±11.7	48.3±10.6	0.854
Weight (kg)	57.0±11.1	54.7±6.3	0.325
Sex (M:F)	8:22	10:20	0.581
Pulse rate	87.2±17.1	90.1±10.1	0.417
RR	20.5±4.0	20.2±3.8	0.792
SPO_2 (%)	99.9±0.4	100.0±0.2	0.412
Visual analog score (0-10)	0 (no pain)	0 (no pain)	
Sedation score (1-5)	1 (awake)	1 (awake)	

SPO_2: Oxygen saturation, RR: Respiratory rate, SD: Standard deviation

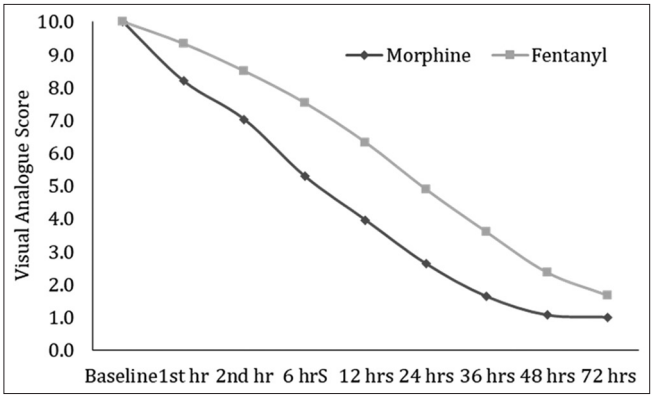

Figure 1: Post-operative visual analog scale scores

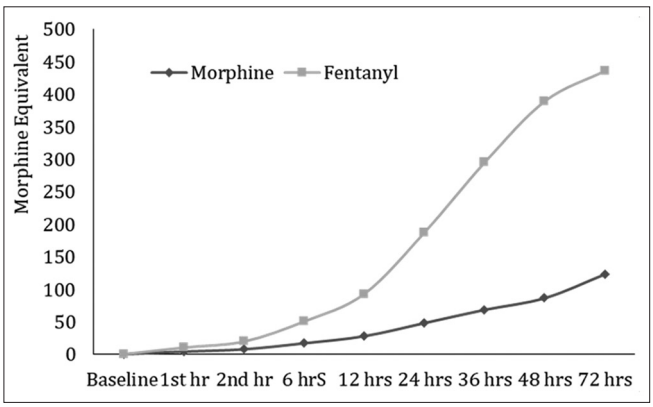

Figure 2: Cumulative analgesic consumption (morphine equivalent/ milligrams)

results revealed a statistically significant higher ($P < 0.05$*) cumulative opioid doses consumption for patients in Group F compared with those in Group M (as MEs; on basis of that (fentanyl 10 mcg = ME) at 1, 2, 6, 12, 24, 36, 48, and 72 h, respectively.

The hourly consumptions of analegesis are shown in Figure 3. Hourly consumption of MEs of fentanyl was significantly higher compared to morphine in 1, 2, 6, 12, 24, 36, and 48 h, respectively. At 72 h, the patients in morphine group consumed less drug (0.5 ± 0.8) in the post-operative period than in fentanyl group (6.1 ± 4.6), and it was statistically significant ($P = 0.05$).

The post-operative sedation score comparison between the groups is shown in Table 2. There was increase in sedation score at 24 and 36 h in fentanyl group (1.6 ± 0.5, 1.2 ± 0.4) compared to morphine group (1.3 ± 0.4, 1.0 ± 0.0) which was statistically significant ($P < 0.05$).

The post-operative pulse rate comparison is shown in Table 3. There was no statistically significant difference between the two groups with regard to pulse rate. The post-operative RRs and the oxygen saturations are shown in Figures 4 and 5. The baseline RRs are 20.5 ± 4.0 and 20.2 ± 3.8 in morphine and fentanyl groups, respectively. There was no statistically

Table 2: Post-operative sedation score

Time (hours)	Mean±SD		
	Group M (morphine)	Group F (fentanyl)	*P*
1	1.2±0.4	1.2±0.4	0.527
2	1.8±0.4	1.7±0.5	0.229
6	1.8±0.4	1.9±0.3	0.723
12	1.6±0.5	1.8±0.4	0.082
24	1.3±0.4	1.6±0.5	0.009
36	1.0±0.0	1.2±0.4	0.019
48	1.0±0.0	1.1±0.3	0.150
72	1.0±0.0	1.0±0.0	0.00

SD: Standard deviation

Table 3: Post-operative pulse rate

Time (hours)	Mean±SD		
	Group M (morphine)	Group F (fentanyl)	*P*
1	87.7±18.4	88.8±12.6	0.788
2	89.5±19.1	92.3±13.2	0.522
6	90.8±15.2	91.6±9.3	0.823
12	92.4±17.1	93.8±11.5	0.725
24	94.1±15.1	93.4±11.8	0.849
36	93.2±15.5	93.8±11.5	0.858
48	91.7±14.7	92.6±9.9	0.773
72	91.6±12.5	91.9±8.0	0.902

SD: Standard deviation

significant difference between the two groups with regard to RR. No patient in the both groups had any episode of respiratory depression (RR <10/min).

The baseline SpO2 is 99.9 ± 0.4and 100.0 ± 0.2 in morphine and fentanyl groups, respectively. SpO2 at the end of 48 h and 72 h were 97.2 ± 1.3 and 97.3 ± 1.0, respectively, in morphine group compared to 97.3 ± 1.4 and 97.4 ± 1.2 in fentanyl group. There was no statistically significant difference between the two groups with regard to SpO2. No patient had any episode of hypoxemia (SaO2 <90%).

The post-operative complications such as ADRs occurred in the both groups are summarized in Table 4. In morphine group, 11 patients had nausea, and 1 patient had vomiting, and in fentanyl group, 7 patients had nausea, and 1 patient had giddiness, postoperatively. None of the patients in either group had hypotension, hypertension, constipation, respiratory depression, and hypoxia. Among the post-operative complications, nausea was higher in morphine group than in fentanyl group (37% vs. 23%), whereas there was no significant difference between the groups with regard to other complications.

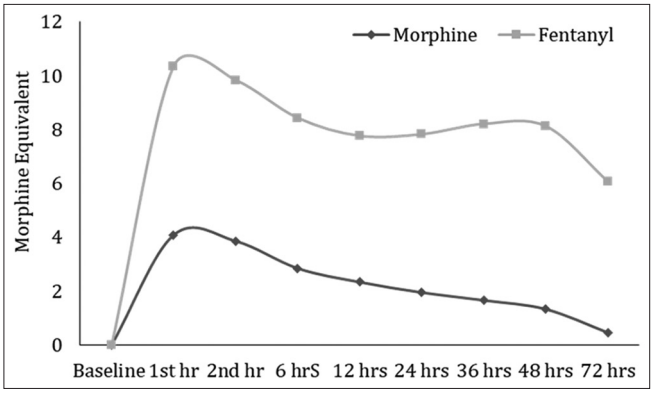

Figure 3: Hourly analgesic consumption in morphine

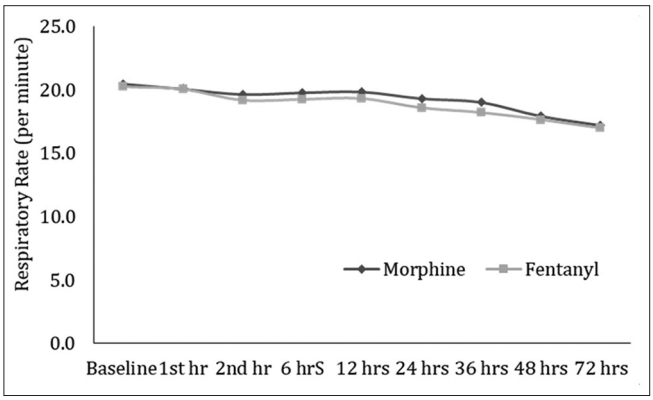

Figure 4: Post-operative respiratory rates

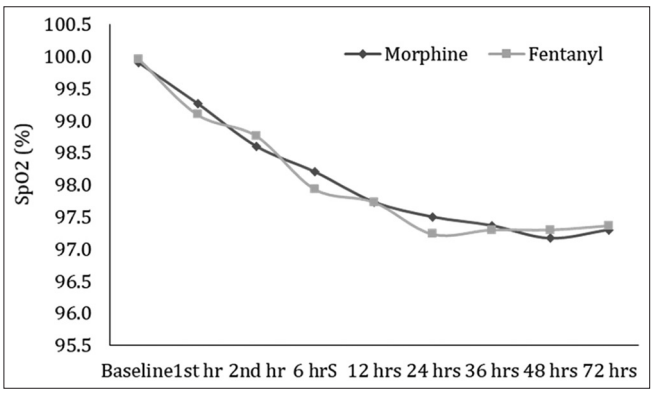

Figure 5: Post-operative oxygen saturation

DISCUSSION

Pain control is a major concern in the post-operative management after major surgeries. Individuals differ in their pain relief requirements. The inability to predict accurately the individual analgesic requirements suggested that a self-administration system by IV PCA may be the most efficient means of achieving analgesic effects and individualizes the therapy. The present study was performed to compare the clinical efficacy and adverse effects of IV PCA morphine and fentanyl in post-operative management of pain. Our study revealed a better analgesia produced from morphine group rather than fentanyl indicated by lower VAS scores (score = 3) at the end of 24, 48, and 72 h. This was consistent with the result of the study conducted by Kim et al. concluding that morphine provides better analgesia than fentanyl Kim et al [12].

Table 4: Post-operative complications

ADRs	Mean±SD		
	Group M (morphine)	**Group F (fentanyl)**	***P***
Nausea (%)	11 (37)	7 (23)	0.27
Vomiting (%)	1 (3)	Nil	0.32
Giddiness (%)	Nil	1 (3)	0.32
Hypo/hypertension	Nil	Nil	-
Hypoxia	Nil	Nil	-
Constipation	Nil	Nil	-
Respiratory depression	Nil	Nil	-
Pruritus	Nil	Nil	-

ADRs: Adverse drug reactions, SD: Standard deviation

In a study done by Howel et al.,[13] the fentanyl group required more supplementary drug, consumed 62.65 mg of fentanyl compared to morphine group (74 mg) at the end of 24 h. However, in our study, cumulative analgesic consumption at the end of 24 h with morphine (48.4 ± 13.8) compared to fentanyl group is 187.7 ± 68.1.

In another study by Woodhouse et al.,[14] the mean VAS was similar in both groups, but total drug consumed by fentanyl group was significantly more (143 ± 86 mg) than morphine group (82 ± 50 mg). In our study, it also has shown similar results by 72 h.

In our study, there was a gradual decrease in hourly consumption of morphine during 72 h. In fentanyl group, also there is a decrease in hourly consumption of MEs of fentanyl till 12 h (10.3 ± 2.0, 9.8 ± 2.1, 8.4 ± 2.9, and 7.8 ± 3.0 ME), but after 12 h, there was an increase in consumption of MEs of fentanyl up to 36 h (7.8 ± 2.8 and 8.2 ± 3.2 ME), followed by gradual decrease in consumption of MEs of fentanyl for next 72 h (8.1± 3.5 and 6.1 ± 4.6 ME). Analysis of hourly consumption of MEs of both drugs showed an acute tolerance with fentanyl but not with morphine.

Regarding the sedation scores, patients were significantly more sedated at 24-36 h assessment in fentanyl group. This corresponds to the increased time period of 12-48 h when the fentanyl requirements were significantly increased than morphine to maintain equivalent analgesic ($P = 0.05$).

In a study by Claxton et al.,[14,15] they found that nausea was more in morphine group than in fentanyl group. In another study by Niiyama et al.,[9] they observed that there was no significant difference in the incident of nausea between the groups. In our study, also the incidence of nausea was higher among patients receiving morphine than those who received fentanyl (37% vs 23 %) but not statistically significant.

The previous studies reported that sedation and life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients while receiving opioids as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. In our study, none of the patients in either group had respiratory depression and hypoxia, hypotension, hypertension, and constipation.[16,17]

CONCLUSION

Morphine provides more effective post-operative analgesia than fentanyl when administered through IV PCA. The adverse events by morphine are less then fentanyl during post-operative period since the patients were self-adjusting the dose. Acute tolerance is seen with fentanyl.

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