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Comparative Study of Intravenous Fentanyl Vs Nebulisation Fentanyl for Postoperative Analgesia in Patients Undergoing Lower Limb Surgeries - A Randomised Controlled Study

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Abstract: ***Introduction: Intravenous administration of Fentanyl is the gold standard treatment for the relief of post-operative pain. Fentanyl being a highly lipophilic drug, pulmonary route of administration provided promising results. Additionally, it is non-invasive, and slow in onset of action. It reaches a therapeutic concentration in less than 2 minutes. Methodology: This is a Prospective randomized controlled trail, among the 60 patients of ASA 1 or 2, admitted for lower limb surgeries randomly divided in two groups with 30 patients in each group. Nebulisation Fentanyl group-4 microg/kg of fentanyl and IV Fentanyl group-2microg/kg were compared for hemodynamic stability, onset and duration of analgesia, Sedation and complications. Results: Baseline characteristics such as Age, Weight and Gender were not significantly different between the groups. Haemodynamic Parameters such as Heart rate, SpO2, respiratory rate, and Systolic, Diastolic and Mean arterial Blood Pressure at baseline were similar. IV fentanyl group produced a slight significant change in hemodynamic parameters such as Heart rate, respiratory rate, and SystolicBlood Pressure. The pain score was significantly lower among the IV fentanyl group compared to the Neb. Fentanyl group and after 15 min post op, the pain score was significantly lower among the Neb. Fentanyl group compared to IV fentanyl group. The Duration of Rescue Analgesia (min) among Neb. Fentanyl group was significantly longer. IV Fentanyl group had significantly higher Nausea / Vomiting. Pruritis and respiratory depression were not significantly different. Conclusion: Administration of Fentanyl via nebulisation can be preferred, over the intravenous administration for its better hemodynamic stability, longer duration of analgesia, without complications. Intravenous administration of Fentanyl can be considered where rapid onset and sedation are needed.***

Keywords: Fentanyl, nebulised fentanyl, IV fentanyl, Post-operative pain relief, Lower limb surgeries

1. Introduction

Fentanyl is a strong agonist at the μ-opioid receptors. Fentanyl is a synthetic opioid analgesic and powerful opioid agonist first synthesized in 1960, that are widely used to complement the general anaesthesia or as primary anaesthetic drugs in very higher doses for the management of pain [(1).] Fentanyl is a synthetic phenylpiperidine-derivative opioid agonist that is structurally connected with meperidine. Fentanyl is 75-125 times highly potent analgesic when compared to morphine [(2)] Fentanyl is used an adjuvant in anaesthetic practice, and as intravenous anaesthetic. Fentanyl acts very quickly within 1-2 minutes, it can cross the blood brain barrier. The duration of analgesic action lasts shortly for 30 to 40 minutes, but the respiratory and CNS depression lasts long. Like other opioids, action of the fentanyl is competitively reversed with naloxone. Due to the high affinity of μ-opioid for Fentanyl, larger naloxone doses are necessary to reverse the drug effects of Fentanyl [(3)]

Fentanyl is the preferred opioid for management of pain, because of its minimal cardiovascular effects, reduced release of histamine, easy and inexpensive to manufacture, and conventionally familiar drug in management of pain [(4)] Intravenous administration of Fentanyl is the gold standard treatment for the relief of post-operative pain. The onset of analgesia is rapid, and have a shorter duration of action, at the same time the complications such as respiratory depression, bradycardia and hypotension are not rare [(3)] Even though the action of Fentanyl is short, the recurrent ventilatory depression reported has been lasting longer [(5).] Moreover, Intravenous (IV) port, causes infections, dislodgments, and distress to the patients.

Other routes of administration of Fentanyl intranasally, inhalational, transdermal, and transmucosal has been widely studied. Fentanyl being a highly lipophilic drug, pulmonary route of administration provided promising results. Additionally, it is non-invasive, and slow in onset of action. It reaches a therapeutic concentration in less than 2 minutes. ([6])

The aim of the study is to compare the effectiveness of nebulised fentanyl with IV fentanyl for post-operative pain relief and side effects in patients undergoing lower limb surgeries.

2. Materials and Methods

60 patients of ASA 1 or 2, admitted for lower limb surgeries under the Department of Anaesthesiology, Jhalawar Medical College & Associated Hospital, Jhalawar (Rajasthan). They

were randomly divided in two groups with 30 patients in each group. **Group I (IV Fentanyl)-**Included 30 patients who received 2microg/kg of fentanyl diluted in 10 ml of normal saline 0.9% intravenously over 2 mins and with 6ml of normal saline 0.9% Nebulized using standard ventimask at a constant flow rate of oxygen at 8-10 l/min for 10 min. **Group N (Fentanyl Nebulization)-**Included 30 patients who received 10 ml of normal saline 0.9% intravenously over 2 mins and with 4 microg/kg of fentanyl in 6ml of normal saline 0.9% Nebulized using a standard ventimask at a constant flow rate of oxygen at 8 – 10 l/min for 10 mins. Preanaesthetic evaluation and Basic investigations has been done before the procedure. Patients with age between 30 to 50 yrs, ASA 1 & 2, Weight between 50 to 80 kg with normal laboratory parameters are included. Patients with ASA 3 or >3, BMI >30, Pregnant or Breast feeding women, Baseline Heartrate <60 beats /min, any hypersensitivity to opoids were excluded from the study.

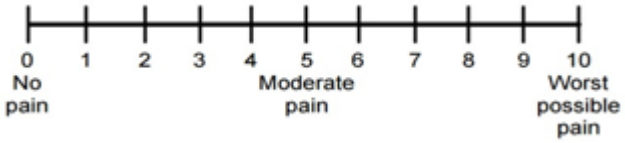
On the day of surgery randomisation was done in the preoperative patient waiting area and patient was explained about the procedure again and informed written consent was taken. Patients were shifted to operating room. On arrival, all standard monitoring techniques were attached, and baseline parameters were recorded. IV line was secured by 18 G cannula and 500 ml Ringer's Lactate solution were started. After preloading with Ringer's Lactate solution 10ml/kg, a subarachnoid block at L3-L4 intervertebral space by Quincke's 25 G spinal needle in sitting position were given, after confirmation of the subarachnoid space 3ml injection 0.5% bupivacaine heavy pushed in the space without any adjuvants.

Patients were made in supine position immediately after the subarachnoid block. The ideal level of blockade needed for the surgery was between T8 and T10. During the time of surgery all the vital parameters were monitored and maintained with in the normal limits. No intraoperative sedation was given. After this the surgery patients were shifted back to postoperative ward in stable condition.

In the postoperative ward, when patient complaints of pain of VNRS score > 4 analgesia was given with nebulization fentanyl or Intravenous fentanyl based on the respective groups, After confirming with normal vital parameters.

Parameters of observation:
Intraoperatively patients vital parameters were observed at different levels. In the postoperative period after giving anaesthesia on complaints of pain the effect of drug was evaluated as different parameters. (1) **Onset of analgesia:** The time from the completion of analgesia (intravenous or nebulization) until VNRS became equal or less than 2.

VNRS (Verbal Numerical Rating Scale)



1) **Duration of analgesia:** The time from the completion of analgesia until the patient's second request of analgesia. Patients vitals will be recorded at the interval of 5min till 30 mins, then at the interval of 15 mins till the need for rescue analgesia
2) **Side effects:** Nausea and vomiting, Bradycardia (heart rate < 60/min), Respiratory depression (respiratory rate < 8 min), Hypotension (Mean arterial pressure < 50mm Hg), Pruritis, Bronchospasm

3. Results

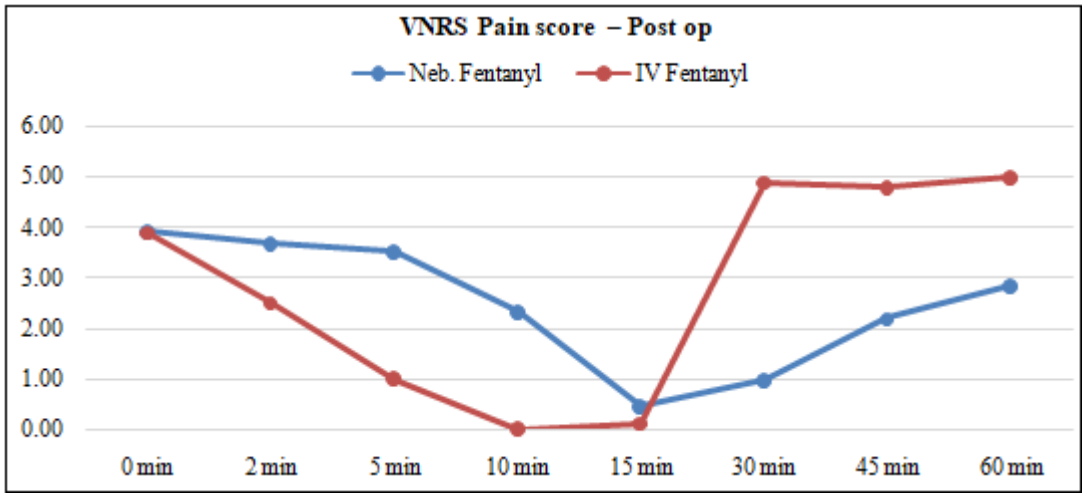
Baseline characteristics such as Age, Weight and Gender were not significantly different between the groups. Haemodynamic Parameters such as Heart rate, SpO2, respiratory rate, and Systolic, Diastolic and Mean arterial Blood Pressure at baseline were similar. The mean VNRS at 0 min among Neb. Fentanyl group was 3.93 (± 0.25) which is higher by 0.03 but not statistically significant compared to 3.9 (± 0.31) in IV Fentanyl group. The mean VNRS at 2 min among Neb. Fentanyl group was 3.7 (± 0.47) which is higher by 1.2 and statistically significant compared to 2.5 (± 0.63) in IV Fentanyl group. The mean VNRS at 5 min among Neb. Fentanyl group was 3.53 (± 0.63) which is higher by 2.53 and statistically significant compared to 1 (± 0.74) in IV Fentanyl group. The mean VNRS at 10 min among Neb. Fentanyl group was 2.33 (± 0.48) which is higher by 2.33 and statistically significant compared to 0 (± 0) in IV Fentanyl group. The mean VNRS at 15 min among Neb. Fentanyl group was 0.47 (± 0.78) which is higher by 0.37 and statistically significant compared to 0.1 (± 0.31) in IV Fentanyl group. The mean VNRS at 30 min among Neb. Fentanyl group was 1 (± 0.87) which is lower by 3.9 and statistically significant compared to 4.9 (± 0.92) in IV Fentanyl group. The mean VNRS at 45 min among Neb. Fentanyl group was 2.2 (± 1.56) which is lower by 2.6 and statistically significant compared to 4.8 (± 0.45) in IV Fentanyl group. The mean VNRS at 60 min among Neb. Fentanyl group was 2.86 (± 1.62) which is lower by 2.14 and statistically significant compared to 5 (± 0) in IV Fentanyl group.

The pain score was initially higher in Neb. Fentanyl group compared to IV fentanyl group and after 15 min post op, the pain score decreased significantly in Neb. Fentanyl group compared to IV fentanyl group.

VNRS Pain score – Post op

	Group	N	Mean	Std. dev.	Mean diff.	p value by 't' test
VNRS at 0 min	Neb. Fentanyl	30	3.93	0.25	0.033	0.647
	IV Fentanyl	30	3.90	0.31		
VNRS at 2 min	Neb. Fentanyl	30	3.70	0.47	1.200	0.001
	IV Fentanyl	30	2.50	0.63		
VNRS at 5 min	Neb. Fentanyl	30	3.53	0.63	2.533	0.001
	IV Fentanyl	30	1.00	0.74		
VNRS at 10 min	Neb. Fentanyl	30	2.33	0.48	2.333	0.001
	IV Fentanyl	30	0.00	0.00		

VNRS at 15 min	Neb. Fentanyl	30	0.47	0.78	0.367	0.021
	IV Fentanyl	30	0.10	0.31		
VNRS at 30 min	Neb. Fentanyl	30	1.00	0.87	3.900	0.001
	IV Fentanyl	30	4.90	0.92		
VNRS at 45 min	Neb. Fentanyl	30	2.20	1.56	2.600	0.001
	IV Fentanyl	5	4.80	0.45		
VNRS at 60 min	Neb. Fentanyl	21	2.86	1.62	2.143	0.001
	IV Fentanyl	1	5.00	0.00		



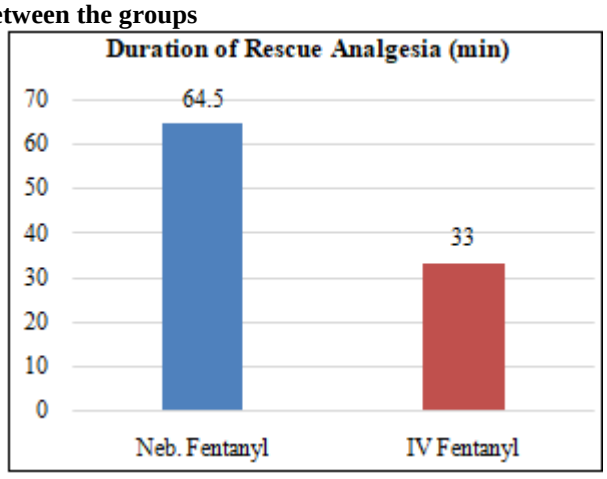
Comparison of Duration of Rescue Analgesia (min) between the groups

The mean Duration of Rescue Analgesia (min) among Neb. Fentanyl group was 64.5 (± 19.75) which is higher by 31.5 and statistically significant compared to 33 (± 7.26) in IV Fentanyl group.

Comparison of Duration of Rescue Analgesia (min) between the groups

	Group	N	Mean	Std. dev.	Mean diff.	p value by 't' test
Duration of Rescue Analgesia (min)	Neb. Fentanyl	30	64.50	19.75	31.500	0.001
	IV Fentanyl	30	33.00	7.26		

Comparison of Duration of Rescue Analgesia (min) between the groups



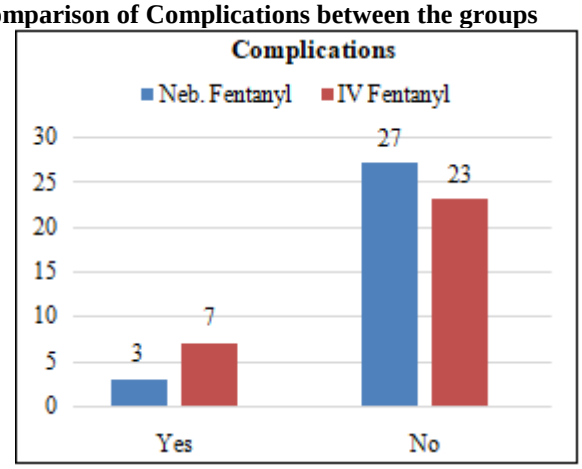
Comparison of Complications between the groups

Comparing the Complications between the groups, 10% of the Neb. Fentanyl group had Complications which is lower but not statistically significant ($p > 0.05$) compared to IV Fentanyl group of whom 23.33% had Complications.

Comparison of Complications between the groups

Complications	Group		Total	p value
	Neb. Fentanyl	IV Fentanyl		
Yes	3 (10%)	7 (23.33%)	10 (16.66%)	0.166
No	27 (90%)	23 (76.66%)	50 (83.33%)	
Total	30 (100%)	30 (100%)	60 (100%)	

Comparison of Complications between the groups



Comparison of Complications profile between the groups

Comparing the Pruritis between the groups, 6.66% of the Neb. Fentanyl group had Pruritis which is lower compared to IV Fentanyl group of whom 10% had Pruritis. Comparing the Nausea / Vomiting between the groups, 3.33% of the Neb. Fentanyl group had Nausea / Vomiting which is lower compared to IV Fentanyl group of whom 20% had Nausea / Vomiting. Comparing the Respiratory Depression between the groups, 0% of the Neb. Fentanyl group had Respiratory Depression which is lower compared to IV Fentanyl group of whom 3.33% had Respiratory Depression.

Complications	Group		Total
	Neb. Fentanyl	IV Fentanyl	
Pruritis	2 (6.66%)	3 (10%)	5 (8.33%)
Nausea / Vomiting	1 (3.33%)	6 (20%)	7 (11.66%)
Respiratory Depression	0 (0%)	1 (3.33%)	1 (1.66%)

4. Discussion

Fentanyl is the preferred opioid for management of pain, because of its minimal cardiovascular effects, reduced release of histamine, easy and inexpensive to manufacture, and conventionally familiar drug in management of pain. [4] Intravenous administration of Fentanyl is the gold standard treatment for the relief of post-operative pain. Other routes of administration of Fentanyl intranasally, inhalational, transdermal, and transmucosal has been widely studied. Fentanyl being a highly lipophilic drug, pulmonary route of administration provided promising results. Baseline characteristics such as Age, Weight and Gender were not significantly different between the groups. Hence the role of confounding bias by these factors can be ruled out.

Intraoperatively: In our study, the Heart rate, SpO2, Systolic, Diastolic and Mean arterial Blood Pressure at baseline, were not significantly different between the two groups. .

Postoperatively: VNRS Pain score: Postoperative pain control is a very vital skill for an anaesthetist and part of the essential anaesthetic care. Various studies have validated the Verbal Numerical rating scale for the measurement of pain. [7, 8]. In our study, the pain score was significantly lower among the IV fentanyl group compared to the Neb. Fentanyl group and after 15 min post op, the pain score was significantly lower among the Neb. Fentanyl group compared to IV fentanyl group.

Duration of Rescue Analgesia (min): In this study, the mean Duration of Rescue Analgesia (min) among Neb. Fentanyl group was 64.5 (± 19.75) which is higher by 31.5 and statistically significant compared to 33 (± 7.26) in IV Fentanyl group. Similarfindings, has been observedby**Anil P Singhet al**, observed that the onset of analgesia was significantly delayed (10 min vs.5 min), duration of the analgesia was significantly longer, among the group received nebulized fentanyl and the level of analgesia was at par. [9] **Reza Ershadet al**, observed that the onset of analgesia was significantly delayed (10 min vs.5 min), duration of the analgesia was significantly longer (90 min vs.30 min), among the group received nebulized fentanyl. [10]

Complications: In this study, 10% of the Neb. Fentanyl group had Complications which is lower but not statistically significant ($p > 0.05$) compared to IV Fentanyl group of whom 23.33% had Complications. IV Fentanyl group had significantly higher Nausea / Vomiting (20%) compared tothe Neb. Fentanyl group (3.33%). Pruritis and respiratory depression were not significantly different. In a study by **Ahmed M. Abd El-Hamid et al**, observed lesser incidence of side effects (bradycardia) among the group received nebulized fentanyl. [11]. **Anil P Singhet al**, observed that the incidence of side effects (respiratory depression, bradycardia and hypotension) was lesser among the group received nebulized fentanyl. [9]

In this study we compared the nebulized fentanyl versus intravenous fentanyl, whereas the study by **aghvendra Singhet al [12],** compared the nebulized fentanyl versus intravenous fentanyl versus intranasal fentanyl and observed that the onset of analgesia was significantly faster among intravenous fentanyl group. The above studies mentioned were conducted in management of the post-operative pain. The following studies were conducted in pain of non-surgical reasons. **James R Miner et al**, observed that the significant relief of pain with inhalational fentanyl in acute pain, and the results were comparable with the intravenous fentanyl, without any adverse effects. [13]. **Joel M Bartfield et al**, observed a significant relief of pain with inhalational fentanyl in abdominal pain, and the results were comparable with the intravenous fentanyl.

5. Conclusion

It is concluded that administration of Fentanyl via nebulisation can be preferred, over the intravenous administration for its better hemodynamic stability, longer duration of analgesia, without complications. Intravenous administration of Fentanyl can be considered where rapid onset and sedation are needed.

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