Original Research Article

Post-operative analgesic efficacy of fentanyl via different routes – A comparative study of nebulisation, intranasal and intravenous routes

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Abstract

Background: Pain is main post operative adverse outcomes 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 effects of fentanyl via nebulisation, intranasal and intravenous routes to provide better analgesia, anxiolysis and sedation to the patient.

Materials and methods: After approval from ethical committee of SPMC, Bikaner and written informed valid consent from patients, sixty patients of either sex belonging to ASA class I and II, were randomised into three group (Group I - Nebulised Fentanyl, Group II - Intranasal Fentanyl, Group III - Intravenous Fentanyl). With all aseptic precaution, subarachnoid block was instilated via 23/25 gauze spinal needle by injecting sufficient dose of bupivacaine heavy 5% to achieve an adequate sensory and motor block for the proposed surgery. When patient complained pain 1st time, fentanyl was given via nebulisation in group I, intranasal in group II, and intravenous in group III with dose 4 mcg/kg, 1.5 mcg/kg, 2 mcg/kg respectively. Patients were assessed for pain by VAS score. For statistical data, SPSS 10.0 software was used.

Results: In present study, Ramsay sedation score, patient satisfaction score and duration of analgesia was better in group II as compared to group I and III. Group III had lesser time of onset of analgesia in comparison to group II and I respectively.

Conclusion: On the basis of analgesic efficacy, we concluded that intranasal group was better than nebulisation and intravenous route.

Key words

Fentanyl, Post-operative analgesia, Intranasal administration, Side-effects.

Introduction

Pain is defined as "unpleasant physical and emotional experience due to tissue damage". Pain is the most frequent cause of suffering and disability.

Good post-operative analgesic management probably carries benefits other than increased patient comfort. The magnitude of the neuroendocrine stress response [1] post-operative pulmonary complications and the incidence of myocardial ischemia can be decreased. Although postoperative pain is arguably the most common clinical problem in our hospitals, it is often dismissed with an order for intermittent intramuscular opiate injections to be given at the discretion of an overworked nursing staff. With this method, pain relief is only satisfactory (i.e. adequate relief without unwanted sedation) for about one-third of the time [2].

Pain is one of the main post operative adverse outcomes causing distress to patients, prolonging hospital stay and increasing the incidence of admissions after surgery [3].

Intravenous (IV) route for fentanyl administration has been the gold standard for post-operative pain relief. However, it is often associated with complications such as respiratory depression, bradycardia and hypotension [4]. The alternative route could be pulmonary drug delivery and Intranasal opioid administration results in a rapid onset of action and a relatively short duration of effect. Fentanyl being highly lipophilic is suitable for use through this route and pulmonary and intranasal administration could be a new promising non-invasive method for systemic fentanyl administration. Nasal route is nowadays widely used for the delivery of various systemically acting drugs. By intranasal administration medicinal substances, fall directly into the systemic circulation in an easy, affordable and painless way [5].

Materials and methods

This study was conducted on 60 cases in the department of anaesthesiology, Sardar Patel Medical College and Associated group of Hospitals Bikaner between March 2014 and August 2015 after taking permission from Institutional Ethical Committee or Research Board. Both male and female patient ranging between the age group of 20 to 60 year belonging to ASA class I and II grades, weighing 40-70 kg, scheduled for either elective or emergency lower abdominal or lower limb surgical procedure which are anticipated to complete within 2 hour under regional anaesthesia were included.

Sixty adult patients of either sex belonging to ASA class I or II were included in study. They were randomized into three groups and an effort was made that the group do not significantly differ with respect to age, weight and height.

Patients with history of allergic reaction to the study drugs, those with significant cardiac diseases, pulmonary diseases, hepatic or renal dysfunction, obese patient BMI >40 (>130% ideal body weight) those with history of chronic use of sedative drugs, epileptic patients all were excluded from this study.

Pre-anesthetic check up was carried out a day before surgery. Patients were kept fasting overnight and the procedure of spinal anesthesia was explained to each patient and written informed consent was taken from the patient and his relatives. Routine lab investigations like hemogram, blood sugar, blood urea, serum creatinine, chest X-Ray and ECG were done.

Standard monitoring was recorded with non-invasive BP, pulse, and SpO_2.

The patient was shifted to the operating room and with all aseptic precaution. Subarachnoid block was instilated via 23 or 25 gauze spinal needle by injecting 3 ml of bupivacaine heavy 5% (plane) in order to achieve an adequate sensory and motor block for the proposed surgery. HR, BP, SpO_2, RR and Anxiety Score were recorded.

The patients were divided randomly into 3 groups of 20patients in each group the control group was included.

Group I - Patients were given fentanyl 4 mcg/kg in 5 ml solution Via nebulisation route.

Group II - Patients were given fentanyl 1.5 mcg/kg (100 mcg in 2 ml solution) via intranasal route.

Group III - Patients were given fentanyl 2 mcg/kg via Intra venous route.

On arrival of the patient in post-operative care unit (PCU), a paramedic blind to the drug alternately allocated patients included in the study with computer assistance into the three groups (Nebulisation, Intranasal and Intravenous respectively).

- For nebulisation, 5 ml of 4 mcg/kg fentanyl was prepared.
- For intranasal, 1.5 mcg/kg of fentanyl was given via Tuberculin Syringe.
- For intravenous route, 2 mcg/kg of fentanyl was filled in the syringe.

Every patient enrolled in the study was given the drug. When complain of pain for first time of VAS Score > 4

In nebulisation group (group-1), patients were nebulised by standard venti mask having nebulisation chamber at a constant flow rate oxygen 8-10 lit/min for 8 min. After nebulisation time of onset of analgesia was calculated. Patients who did not get relief in pain even after 15 min. from the start were excluded from the study.

In intranasal group (group – II), patients were reclined at 45 degree and syringe was in horizontal position and content was expelled into the nares in one rapid dose and dose was divided equally between two nares.

In group III Patient were given intravenous fentanyl through IV cannula. The following parameters were noted. Patients were assessed for pain by VAS Score. VAS is a sensitive measure for pain intensity. A 10 cm horizontal line labeled as "No pain" at one end and "Worst pain imaginable on the other end. Patient was asked to mark on the line where the pain lies. No pain, Mild pain, Moderate pain, Severe pain, Worst pain.

Sedation Score by Ramsay Sedation Scale.

- Patient is anxious and agitated or restless, or both
- Patient is co-operative, oriented, and tranquil
- Patient responds to commands only
- Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
- Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
- Patient exhibits no response

Time of onset of analgesia, duration of analgesia, patient satisfaction score was done by Likert Scale. Likert scaling is a bipolar scaling method measuring either positive or negative response to a statement. Sometimes an even-point scale is used, where the middle option of "Neither agree nor disagree" is not available.

The format of a typical five-level Likert Scale was Strongly disagree, Disagree, Neither agree nor disagree, Agree, Strongly agree

Patients who were not relieved of pain even after 15 min from start of study were excluded from the study. Heart rate, blood pressure and arterial oxygen saturation were monitored at initially at 5, 10 , 15 min. interval for one hour then 30 min.

interval for 2 hours than hourly till 2nd dose of analgesic was required. Time of 2nd dose requirement was noted.

Any adverse effects (Complications) such as Nausea vomiting, respiratory depression, urinary retention, constipation, pruritus and any other complication were noted.

The data obtained were statistically analysed. Repeated data were analysed using one-way repeated measures analysis of variance, Chi-square test ANOVA test. For statistical data, SPSS 10.0 software was used. $P<0.05$ was considered to be statistically significant.

Primary outcome

To assess the analgesic efficacy of nebulised fentanyl and intranasal fentanyl in comparison to Intravenous fentanyl for post-operative pain relief after lower abdominal and lower limb surgery.

Secondary outcome

To measure the side-effects of nebulised and intranasal fentanyl administered to the patients.

Results

Overall, 60 consecutive patients were enrolled in the study. These were randomised in three groups (Nebulisation, Intranasal and Intravenous) with 20 patients in each group. Of the 60 patients enrolled in the study, data of 60 patients were available for analysis, 20 received nebulised fentanyl, 20 received intranasal fentanyl and 20 received IV fentanyl. The groups were similar in terms of demographics. The mean age of patients among all the groups were comparable and was not statistically significant. The distribution of males to females in all four groups ranged from 33.3% to 67.7%, which had no statistical significance. Patients were assessed for sedation via Ramsay sedation score which was maximum at 5 min. In groups I and II, there was a slow rise in the sedation score but it was always less than in group III (**Table - 1**). Adverse effects in groups Nebulisation and Intranasal were less compared with the Intravenous group though statistically insignificant (**Table - 2**). No enrolled patient had clinically significant hemodynamic instability or respiratory depression.

Table – 1: Ramsay Sedation Score during study.

Ramsay Sedation Score	**Groups**						**Total**	
	I		**II**		**III**			
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
1	5	25.0	0	-	6	30.0	11	18.3
2	15	75.0	20	100	14	70.0	49	81.7
Total	20	100	20	100	20	100	60	100
Mean	1.75		2.00		1.70			
SD	0.44		0.00		0.47			
			T		P			
Group I Vs II			2.517		0.016			
Group I Vs III			0.346		0.731			
Group II Vs III			2.854		0.007			

Patients' self-evaluation of satisfaction allowed us to understand their perception of the pain they experience so that we may initiate positive outcomes, and meet or exceed the patients' highest expectations in the adequacy of pain control All the differences were found statistically highly significant ($p<0.001$) on comparing group I Vs II, group I Vs III and group II Vs IIIs (**Table - 3**). Patients were assessed for pain via VAS statistically significant mean VAS change started at 5 min and continued until 15 min ($P < 0.005$) (**Table - 4**).

Table – 2: Incidence of adverse effect in various groups.

Complications	Groups						Total	
	I		II		III			
	No.	%	No.	%	No.	%	No.	%
Constipation	0	-	0	-	1	5.0	1	1.7
Nausea, Vomiting	1	5.0	0	-	0	-	1	1.7
Respiratory Distress	0	-	0	-	2	10.0	2	3.3
No Adverse Effect	19	95.0	20	100	17	85.0	56	93.3
Total	20	100	20	100	20	100	60	100
χ^2	8.250							
P	0.220 NS							

Table – 3: Patient Satisfaction in Various groups.

Satisfaction Score	Groups						Total	
	I		II		III			
	No.	%	No.	%	No.	%	No.	%
1	1	5.0	0	-	0	-	1	1.7
2	17	85.0	0	-	5	25.0	22	36.7
3	2	10.0	1	5.0	10	50.0	13	21.7
4	0	-	14	70.0	5	25.0	19	31.7
5	0	-	5	25.0	0	-	5	8.3
Total	20	100	20	100	20	100	60	100
Mean	2.05		4.20		3.00			
SD	0.39		0.52		0.73			
			T		P			
Group I Vs II			14.681		<0.001			
Group I Vs III			5.146		<0.001			
Group II Vs III			6.000		<0.001			

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. Ramsay Sedation Score in Intravenous group reached peak at 5 min and decreased after 1 hour. In Nebulisation and intranasal group, it increased after 10 min in dose dependent manner but was always less than Intravenous group during study. This finding can be attributed to slow rise in peak plasma concentration by inhalational and intranasal administration of fentanyl. This correlates with the finding by previous studies Peach, et al. [6] and Foster, et al. [7] that maximum serum concentration of fentanyl is reached at 13 min after intranasal administration as compared to IV administration (2-3 min).

Table - 4: Changes in mean VAS.

Duration of Analgesia (hours)	Groups						Total	
	I		II		III			
	No.	%	No.	%	No.	%	No.	%
4.50	2	10.0	0	-	0	-	2	3.3
5.00	3	15.0	0	-	6	30.0	9	15.0
5.50	2	10.0	1	5.0	5	25.0	8	13.3
6.00	5	25.0	4	20.0	5	25.0	14	23.3
6.50	7	35.0	3	15.0	1	5.0	11	18.3
7.00	1	5.0	1	5.0	3	15.0	5	8.3
7.50	0	-	8	40.0	0	-	8	13.3
8.00	0	-	3	15.0	0	-	3	5.0
Total	20	100	20	100	20	100	60	100
Mean	5.88		7.00		5.75			
SD	0.74		0.79		0.70			
			T		P			
Group I Vs II			4.630		<0.001			
Group I Vs III			0.549		0.586			
Group II Vs III			5.28		<0.001			

No major adverse effects like respiratory depression; hypoxia or bronchospasm were observed in intranasal group. Side-effects such as constipation, respiratory depression, nausea and vomiting were observed in nebulisation and intravenous groups and were dose dependent. This correlates with the findings study conducted by Cheng and Li [8] who observed the effectiveness and adverse reactions of fentanyl used by nasal infusion or intravenous injection in post-operative analgesia in pediatric patients.

Evaluation of patient satisfaction with postoperative pain control guides quality improvement to strengthen the level of pain relief and improve care. The patient satisfaction score in our study was good, Mean satisfaction score in group I was 2.05±0.39, in group II 4.20±0.52 while in group III, 3.00±0.73. All the differences were found statistically highly significant ($p<0.001$) on comparing group I Vs II, group I Vs III and group II Vs IIIs. This correlates with the findings study conducted by Silvasti, et al. [9] compared the efficacy, safety, side effects and patient satisfaction in Continuous epidural analgesia with bupivacaine-fentanyl versus patient-controlled analgesia with i.v. morphine for postoperative pain relief after knee ligament surgery.

The duration and quality of analgesia evidenced by change in VAS was dose dependent and after nebulisation by 4 μg/kg fentanyl and intranasal by 1.5 μg/kg fentanyl, quality was equivalent to 2 μg/kg IV fentanyl. But the duration of analgesia in our study was 7.00 ± 0.79 hours in intranasal group, 5.88 ± 0.74 hours in nebulisation group and 5.74 ± 0.70 hours in intravenous group, which is statistically significant (<0.001) when compared intranasal group with nebulisation and intravenous group. This correlates with the finding Peach, et al. [6] studied two new formulations of nasal fentanyl spray. They concluded that these formulations of fentanyl, delivered as nasal spray, have potential clinical utility. Singh, et al. [4] compared the efficacy of nebulised fentanyl with IV fentanyl for post-operative pain relief in lower abdominal surgery. They studied that nebulisation with 4 μg/kg fentanyl may be used as an alternative to IV 2 μg/kg fentanyl for adequate post-operative pain relief.

Conclusion

From our study we concluded that Intranasal fentanyl provides prolong duration of analgesia but onset is delayed and intravenous route provide early onset of analgesia but duration is much less. Intranasal route provide better patient satisfaction than intravenous and nebulisation group. Patients in intranasal group had significantly very less or no adverse effects. Thus, from our study and observation we can conclude that fentanyl via intranasal route in dose of 1.5 mcg/kg is better, more effective and safe as compared to intravenous and nebulisation route. As our study has been conducted in small group of 60 patients, further studies and references are required to establish the use of fentanyl via intranasal route in postoperative analgesia in patients undergoing lower limb and lower abdomen surgeries under spinal anaesthesia.

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