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Nebulized Fentanyl for Postoperative Pain Relief in Lower Abdominal Surgeries

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Abstract: ***Fentanyl is much more potent than morphine. Intravenous (IV) route for fentanyl administration has been the god standard for postoperative pain relief. Fentanyl is often associated with complications such as respiratory depression, bradycardia and hypotension. Fentanyl being highly lipophilic is suitable for use through pulmonary drug delivery route and pulmonary administration could be a new promising non-invasive method for systemic fentanyl administration. Further, it has been observed that on inhalation, fentanyl is absorbed rapidly and reaches maximum serum level in approx. 2minutes. The aim of this study is to compare the analgesic efficacy of nebulised fentanyl with IV fentanyl for postoperative pain relief in lower abdominal surgery. The study design is a prospective, randomised clinical investigation. The sample size for the study is 100 patients, in two groups i.e, group C (control) and group N (nebulisation). Patients between the age group of 18-50 years of either gender, ASA physical status I or II, and who received spinal anesthesia without any intra operative adjuvant as analgesic are included in inclusion criteria. Patient who refuse to have regional anesthesia; pregnant or breast feeding women; with morbid obesity, respiratory, hepatic and renal insufficiency and who already on chronic analgesic use are included in exclusion criteria. The data obtained is statistically analysed by using chi-square test and students' unpaired t-test. The values are found to be significant statistically at p<0.05 level. The final results are in favour of nebulised fentanyl as a better mode of postoperative pain relief measure and is associated with minimal side effects as compared to the intravenous route of administration. The scope of the study is extended to the pediatric age groups for better pain relief. Here, the major limitation is that the non-cooperation of patients.***

Keywords: Postoperative Analgesia; Fentanyl

1. Introduction

Pain is one of the commonest symptoms of patients admitted to hospital. This should be managed safely and effectively not only from humane and patient comfort perspective but also for better overall care and healing of ill patients. There is heightened attention to pain management particularly after surgical interventions and procedures in recent times as we have better understanding of acute pain physiology, its complications and management modalities [1].Intravenous (I.V) analgesia is one of the most commonly used strategies in modern clinical practice for controlling postoperative pain. It involves intravenous administration of analgesics like NSAIDs and opioids.Rapid delivery of potent opioids to the systemic circulation is an important feature for the effective treatment of acute and acute-on-chronic breakthrough pain [2, 3, 4].Fentanyl is a potent, synthetic opioid analgesic with a rapid onset and short duration of action. Fentanyl has been delivered via the sublingual, buccal, and inhaled routes [2, 5, 6, 7]. Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist. It is structurally related to mepiridine. Fentanyl is much more potent than morphine. It is strong agonist at the mu-opioid G-protein couple receptors which inhibit pain neurotransmitter release by decreasing intracellular calcium levels.Intravenous (I.V) route of administration has been the gold standard for post-operative pain relief although, it is associated with complications like bradycardia, respiratory depression and hypotension.Inhalation or pulmonary drug delivery is a potentially useful alternative to the intravenous route for drug delivery. Fentanyl is highly lipophilic which makes it suitable for use through this route and the pulmonary administration could be a promising non-invasive method for systemic fentanyl administration.Few similar studies published have shown significant postoperative analgesia with nebulized fentanyl [8, 9, 10]. Hence, the aim of this study was to evaluate and compare the efficacy of nebulized fentanyl with intravenous fentanyl for postoperative analgesia in patients undergoing lower abdominal surgery under spinal anaesthesia.

2. Methods

This study is a randomized control study, conducted by the Department of Anaesthesiology, Acharya Vinoba Bhave Rural Hospital, Datta Meghe Institute of Medical Sciences, Sawangi (Meghe), Wardha between April 2014 to April 2016. It was approved by the Institutional Ethical Committee. An informed written consent was taken from all the patients included in this study. 100 American Society of Anaesthesiologists Grade I and II patients of either gender between 18-50 years of age who were scheduled for lower abdominal surgery under spinal anaesthesia, after due explanation were included for the study. Patients refusing spinal anaesthesia, pregnant or breast feeding women, morbid obese patients, respiratory, hepatic, cardiac and renal insufficiency, addiction or hypersensitivity to opioids were excluded. Those patients who were already on chronic analgesic use and the patients who received intraoperative analgesics and those who did not give consent for the study were also excluded from this study.

There were two study groups: I.V fentanyl group, Group C (control) and Nebulized fentanyl, Group N (study group). The enrolled patients underwent 60-90 minutes of surgery under spinal anaesthesia with 12.5 mg bupivacaine. Patients were shifted to the post anaesthesia care unit (PACU), after completion of the surgery. Patients were monitored for oxygen saturation (SpO_2), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and respiratory rate (RR), after shifting to PACU initially at 5, 10 and 15 minutes then at an interval of 15 minutes up to 60 minutes. After that, once the patients complained of pain which was assessed by Verbal Numerical Rating Scale (VNRS), they were given the study drug according to their groups, as 4 ml of 2 mcg/kg intravenous fentanyl in control group (Group C) and 5 ml of 4 mcg/kg nebulized fentanyl in

study group (Group N), respectively. The quantity was 1 ml more for the nebulisation group to compensate for the loss of the drug through nebulisation and in the upper airway. Patients were nebulized through a nebulizer at a constant flow rate of oxygen 8 L/min for 8 min. Onset time of analgesia was calculated after completion of nebulisation. Once the study drug was given to the patients on their demand, they were monitored for sedation by Ramsay Sedation Score (RSS) and side effects of the drug along with the other parameters like SpO_2, HR, SBP, DBP and RR. Upon further complaint of pain which was assessed by VNRS, analgesia was provided to the patients according to their groups. Patients, who were not relieved of pain even after 15 min from start of study, received 15 mg/kg IV paracetamol and were excluded from the study. Patients received IV diclofenac 75mg as the reservoir analgesic at the time of pain. The onset and duration of analgesia was noted in both the groups, Group C and Group N.Patients were assessed for pain by VNRS (0 - no pain, 1- mild pain, 2- moderate pain, 3- severe pain), sedation by Ramsay sedation scale (RSS) (1 - anxious/restless or both 2 - cooperative, oriented and tranquil responding to command; 3 - brisk response to stimulus; 4 - sluggish response to stimulus; 5 - no response to any stimulus) and side effects like nausea, vomiting, pruritis, sedation, confusion, dry mouth, hallucination, delirium, hyperalgesia, seizures, respiratory depression and bradycardia were assessed. The data obtained was statistically analyzed using descriptive and inferential student's unpaired t test and chi-square test with SPSS 17.0 version.

3. Results

Overall, 100 patients were enrolled in this study who were randomized into two groups (Group C and group N) with 50 patients in each group. The groups were similar in terms of demographic data. The mean age, distribution of males to females and the mean weight of the patients were comparable and was statistically insignificant (Table no. 1).In Group C, the mean pain scores (VNRS scores) decreased at 65 minutes, 95 minutes, 125 minutes and 155 minutes, which shows that the patients were relieved of pain and it was observed that patients complained of pain at every 30 minutes after the administration of the drug. In Group N, the mean pain scores decreased at 75 minutes, 110 minutes, 130 minutes and 170 minutes, when the patients were relieved of pain. It was observed that the pain intensity was less in Group N when compared to Group C. Most of the patients did not have any pain after the administration of first dose of analgesic. The mean pain scores were found to be non-significant at 75 minutes, 105 minutes, 135 minutes, 165 minutes, 225 minutes and 240 minutes as the patients were completely relieved of pain (Table no.2). In Group C, it was observed that the peak sedation occurred after 5 minutes of administration of the drug. In Group N, the peak sedation was observed after 10-15 minutes of nebulization. The patients in Group N were found to be less sedated when compared to Group C (Table no.2). Adverse effects in Group N were experienced late and were less than Group C (Table no.3). No enrolled patient had clinically significant haemodynamic instability.

Table 1: Demographic data of the patients

Demographic data of the patients					
Group	Age(years) (mean+SD)	Weight (Kg)	Male	Female	P value
C(n=50)	36.18±8.01	50.84±5.60	25	25	NS
N(n=50)	30.04±6.42	53.08±4.19	25	25	
Group C–Control (IV fentanyl 2µgkg); Group N-Fentanyl nebulization@ 4µgkg. NS-Not Significant (p>0.05); SD-Standard Deviation;IV-Intravenous					

Table 2: Comparison of mean value of VNRS and RSS in two groups at the time and after giving the study drug

Time Interval	VNRS			RSS		
	Group C	Group N	p-value	Group C	Group N	p-value
60 min	1.14±1.46	1.08±1.44	0.05, NS	0.38±0.49	0.0±0.0	0.005, NS
65 min	0.48±0.67	0.72±0.96	0.10, S	1.14±1.46	0.36±0.48	0.005, NS
70 min	0.10±0.30	0.36±0.48	0.01, S	0.76±0.97	0.72±0.96	0.005, NS
75 min	0.00±0.00	0.00±0.00	0.05, NS	0.0±0.0	0.36±0.48	0.01, S
80 min	1.00±0.00	0.34±0.47	0.01, S	0.0±0.0	0.0±0.0	0.005, NS
85 min	2.00±0.00	0.68±0.95	0.05, NS	0.0±0.0	0.0±0.0	0.005, NS
90 min	3.00±0.00	1.02±1.42	0.10, S	1.00±0.0	0.0±0.0	0.005, NS
95 min	1.08±0.27	0.68±0.95	0.01, S	3.00±0.0	0.34±0.47	0.01, S
100 min	0.10±0.27	0.34±0.47	0.05, S	1.96±0.20	0.68±0.95	0.005, NS
105 min	0.00±0.00	0.00±0.00	0.005, NS	0.0±0.0	0.34±0.47	0.01, S
110 min	1.00±0.00	0.30±0.46	0.01, S	0.0±0.0	0.0±0.0	0.005, NS
115 min	2.00±0.00	0.60±0.92	0.005, NS	0.0±0.0	0.0±0.0	0.005, NS
120 min	3.00±0.00	0.90±1.37	0.10, S	1.00±0.0	0.0±0.0	0.005, NS
125 min	1.12±0.32	0.60±0.92	0.01, S	3.00±0.0	0.30±0.46	0.01, S
130 min	0.12±0.32	0.30±0.46	0.10, S	1.96±0.20	0.60±0.92	0.005, NS
135 min	0.00±0.00	0.00±0.00	0.005, NS	0.0±0.0	0.30±0.46	0.10, S
140 min	1.00±0.00	0.34±0.47	0.01, S	0.0±0.0	0.0±0.0	0.005, NS
145 min	2.00±0.00	0.68±0.95	0.005, NS	0.0±0.0	0.0±0.0	0.005, NS
150 min	3.00±0.00	1.02±1.42	0.10, S	1.00±0.0	0.0±0.0	0.005, NS
155 min	1.12±0.32	0.68±0.95	0.005, NS	3.00±0.0	0.34±0.47	0.01, S
160 min	0.12±0.32	0.34±0.47	0.05, S	1.96±0.20	0.68±0.95	0.005, NS
165 min	0.00±0.00	0.00±0.00	0.005, NS	0.0±0.0	0.34±0.47	0.01, S
170 min	1.00±0.00	0.36±0.48	0.01, S	0.0±0.0	0.0±0.0	0.005, NS

175 min	2.00±0.00	0.72±0.96	0.005, NS	0.0±0.0	0.0±0.0	0.005, NS
180 min	3.00±0.00	1.12±1.42	0.10, S	0.0±0.0	0.0±0.0	0.005, NS
195 min	0.00±0.00	0.60±0.69	0.01, S	0.0±0.0	0.36±0.48	0.01, S
210 min	0.00±0.00	0.80±1.27	0.01, S	0.0±0.0	0.0±0.0	0.005, NS
225 min	0.00±0.00	0.00±0.00	0.005, NS	0.0±0.0	0.24±0.43	0.01, S
240 min	0.00±0.00	0±0	0.005, NS	0.0±0.0	0±0	0.005, NS

Table 3: Comparison of side effects in two groups at the time and after giving the study drug

Time Interval	GROUP C								GROUP N							
	Nausea & vomiting		Pruritis		Sedation		Respiratory Depression		Nausea & vomiting		Pruritis		Sedation		Respiratory Depression	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
70 min	9	18	17	34	17	34	3	6	-	-	-	-	-	-	-	-
80 min	-	-	-	-	-	-	-	-	14	28	11	22	0	0	0	0
100 min	13	26	22	44	25	50	10	20	-	-	-	-	-	-	-	-
110 min	-	-	-	-	-	-	-	-	15	30	11	22	0	0	0	0
130 min	10	20	18	36	19	38	3	6	-	-	-	-	-	-	-	-
140 min	-	-	-	-	-	-	-	-	13	26	10	20	0	0	0	0
160 min	13	26	23	46	27	54	12	24	-	-	-	-	-	-	-	-
170 min	-	-	-	-	-	-	-	-	1	2	1	2	0	0	0	0
210 min	11	22	21	42	23	46	9	18	-	-	-	-	-	-	-	-
240 min	-	-	-	-	-	-	-	-	4	8	6	12	0	0	0	0

4. Discussion

This study enrolled 100 patients undergoing lower abdominal surgery under spinal anaesthesia. The patients were given nebulised fentanyl for postoperative pain relief at the onset of pain. The enrolled patients were given nebulized fentanyl (Group N) at 4mcg/kg which was compared with intravenous fentanyl (Group C) at 2mcg/kg. The concentration of fentanyl through nebulization was kept higher considering the wastage of the drug in nebulization and upper airway.

In this study, it was found that the quality of analgesia after nebulisation with 4mcg/kg fentanyl as evidenced by VNRS was effective, although the onset of action of the drug (Nebulized fentanyl) is delayed to 10 minutes after the administration of the study drug. It was also found that the duration of pain relief in the nebulisation group was prolonged when compared with the intravenous group (90minutes vs. 30minutes).

From RSS, it was found that in control group (Group C), it reached the peak at 5 minutes after the administration of the drug. However, in the nebulisation group (Group N), it was found that it increased after 10 minutes of administration.

In the present study, the oxygen saturation was compared between the two groups (Group C and Group N) and it was found to be statistically significant after 5 minutes of administration of the study drug in Group C, as the patients showed fall in oxygen saturation whereas in Group N, the patients showed no fall in oxygen saturation after administering the drug through the nebulized route suggesting that nebulized fentanyl (study group) was better when compared to intravenous fentanyl (control group). We observed a stable heart rate, respiratory rate and blood pressure in the nebulization group when compared to intravenous group.

The enrolled patients in this study showed no major adverse effects like respiratory depression, hypoxia or bronchospasm or bradycardia. However, the side effects like nausea, vomiting, pruritis, sedation were found to more in control group when compared to study group.

Overall, this study revealed that nebulized fentanyl is more effective with a longer duration of analgesia and with fewer side effects and is better tolerated by the patients.

However, there are some limitations to this study such as a small sample size, restricted group of enrolled patients such as including only those patients undergoing lower abdominal surgery under spinal anaesthesia and also this study is limited by the fact that the success with pulmonary administration of opioid analgesics may be due to the complexity of the apparatus, and the difficulty of timing inspiration of the drug delivery systems used.

5. Conclusions

The present study shows that nebulized fentanyl at 4mcg/kg produces effective postoperative analgesia with longer duration of action and with minimal adverse effects.

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