

# Nebulised fentanyl for post-operative pain relief, a prospective double-blind controlled randomised clinical trial

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## ABSTRACT

**Background and Aim:** Intravenous (IV) route for fentanyl administration is the gold standard for post-operative pain relief, but complications such as respiratory depression, bradycardia and hypotension have limited this route. The aim of this randomised controlled trial was to compare the efficacy of nebulised fentanyl with IV fentanyl for post-operative pain relief after lower abdominal surgery. **Methods:** In the post-operative care unit, at the time of first onset of pain (visual analogue scale- VAS score > 4) patients were randomised into three groups and fentanyl was administered either IV 2 µg/kg or by nebulisation of solution containing 3 or 4 µg/kg fentanyl over 8 min in 90 patients divided into three groups of 30 each. Observation were made for pain relief by visual analogue scale score 0-10. Adverse effects such as respiratory depression, bradycardia and hypotension were also recoded. Statistical analysis was performed using Medcalc software version 12, 2012. (MedCalc Software, Ostend, Belgium). **Results:** In the nebulisation group, it was observed that the analgesic efficacy of fentanyl was dose dependent with a delayed onset of analgesia (10 min vs. 5 min). Nebulisation with 4 µg/kg fentanyl produced analgesia at par to 2 µg/kg IV fentanyl with prolonged duration (90 min vs. 30 min) and with significantly less adverse effects. **Conclusions:** This study shows 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.

**Key words:** Fentanyl, post-operative analgesia, pulmonary administration, side-effects

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## INTRODUCTION

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. The alternative route could be pulmonary drug delivery. Fentanyl being highly lipophilic is suitable for use through this 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 approximately 2 min.<sup>[1]</sup> Few studies published have shown significant post-operative pain relief

with nebulised fentanyl.<sup>[2-4]</sup> Chrubasik *et al.* reported results using another drug, morphine and found that morphine nebulisation was as effective as IV morphine for pain relief after abdominal surgery.<sup>[5]</sup> Thus, the aim of this study was to compare the analgesic efficacy of nebulised fentanyl with IV fentanyl for post-operative pain relief in lower abdominal surgery. If successful, this would be a new non-invasive technique of post-operative analgesia with minimal or no side-effects compared with the standard IV route.

## METHODS

This prospective double-blind randomised control clinical trial was conducted by the Department of

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Anaesthesiology in collaboration with the Department of Surgical Oncology at our Institute between January 2010 and June 2011. It was approved by the Institutes' Review Board and Ethical Committee. An informed written consent was taken from all the patients included in the study. Ninety American Society of Anaesthesiologists Grade I or II patients of either gender between 20 and 40 years of age scheduled for lower abdominal surgery under regional anaesthesia, able to comprehend assessment scales after due explanation were selected for study. Pregnant or breast feeding women, patients with morbid obesity, respiratory, hepatic and renal insufficiency, addiction or hypersensitivity to opioids were excluded from study. Those already on chronic analgesic use and those not consenting for the study were also excluded from the study.

There were three study groups: IV fentanyl group C (control) and two nebulisation groups (NI and NII). Patients underwent 60-90 min of surgery under spinal anaesthesia with 12.5 mg Bupivacaine under sedation by maintaining Bi spectral index score of 70-80 with infusion midazolam perioperative.

Power of study was kept 80%, level of significance 5% at two-tailed test. Efficacy of Fentanyl was considered 100% by IV route (control group) and in nebulisation group it was taken as 75%. With above consideration sample size came out 26 patients in each group by taking ratio 1:1. Assuming treatment failure rate of 15% in nebulisation group, sample size was kept at 30 (26 + 4) in each group.

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 (C, NI and NII respectively). Fentanyl solution was prepared by a second paramedic as 4 ml for IV and 5 ml for nebulisation of each enrolled patient in respective groups. The quantity was 1 ml more for the nebulisation groups to compensate for the loss of the drug through the ventimask during nebulisation and in the upper airway. Every patient enrolled in the study received the labelled drug by IV or nebulisation routes whenever the patient complained of pain for the first time of visual analogue scale (VAS) score >4 in PCU.

Concentration of fentanyl was kept as 2 µg/kg in IV solution for group C and nil in IV solution for groups NI and NII patients. Concentration of

fentanyl in nebulisation solution was 3 µg/kg and 4 µg/kg respectively for groups NI and NII and nil in nebulization solution for group C patients. Patients were nebulised by a standard ventimask having nebulisation chamber at a constant flow rate of oxygen 8-10 l/min for 8 min. After completion of nebulisation, onset time of analgesia was calculated in nebulisation group. Upon further complaint of pain with VAS score >4, analgesia was provided by the second paramedic of routine posting as per unit protocol. 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 were observed continuously and data was recorded initially at 5, 10 and 15 min then at interval of 15 min up to 1 h and at 30 min interval until completion of study by a resident doctor blind to the groups. Patients were assessed for pain by VAS (0 - no pain, 10 - maximum imaginable 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), nausea vomiting (0 - no symptoms; 1 - nausea, i.e., subjective unpleasant sensation with awareness of urge to vomit; 2 - retching, i.e., spasmodic contraction of oesophagus, abdominal wall and diaphragmatic muscle without expulsion of gastric content; 3 - vomiting, i.e., forceful expulsion of gastric content), heart rate, respiratory rate, non-invasive blood pressure, oxygen saturation and pruritus.

The data obtained were statistically analysed. Repeated data were analysed using one-way repeated measures analysis of variance, Chi-square test and Student's t-tests as appropriate using Medcalc software version 12, 2012.  $P < 0.05$  was considered to be statistically significant.

Primary outcome: To assess the analgesic efficacy of nebulised fentanyl in comparison to IV fentanyl for post-operative pain relief after lower abdominal surgery.

Secondary outcome: To measure the side-effects of nebulised fentanyl administered to the patients.

## RESULTS

Overall, 90 consecutive patients were enrolled in the study. These were randomised in three groups

(groups C, NI and NII) with 30 patients in each group. Of the 90 patients enrolled in the study, data of 83 patients were available for analysis, 55 received nebulised fentanyl and 28 received IV fentanyl. The groups were similar in terms of demographics. The mean age of patients among all the groups are comparable and is not statistically significant. The distribution of males to females in all four groups ranged from 40% to 60%, which had no statistical significance [Table 1]. Statistically significant mean VAS change started at 5 min and continued until 15 min ( $P < 0.005$ ) [Table 2]. VAS decreased until 30 min in group C and until 90 min in groups NI and NII. In group C, sedation score was maximum at 5 min. In groups NI and NII, there was a slow rise in the sedation score but it was always less than in group C [Table 3]. Adverse effects in groups NI and NII were less compared with the control (group C) though statistically insignificant [Table 4]. No enrolled patient had clinically significant hemodynamic instability or respiratory depression.

## DISCUSSION

The present study enrolled patients who were operated under regional anaesthesia to avoid emergence delirium effect of general anaesthesia. Patients were nebulised with fentanyl post-operatively at onset of pain as few studies have suggested that nebulised fentanyl has a good analgesic efficacy.<sup>[2-4]</sup> Patients in the nebulisation groups (NI and NII) were nebulised with two doses of fentanyl, i.e. 3 µg/kg and 4 µg/kg respectively compared with IV fentanyl 2 µg/kg in control group (group C) considering wastage of drug in nebulisation chamber and upper airway.

In our study, onset of analgesia was delayed in the nebulisation group (10 min vs. 5 min) which correlates with the finding of the previous studies that maximum serum concentration of fentanyl is reached at 13 min after intranasal administration as compared to IV administration<sup>[6]</sup> (2-3 min), but contradicts the finding of Mather<sup>[7]</sup> who reported that inhaled fentanyl reached to therapeutic level in blood stream as quickly as IV dosing. This discrepancy needs further evaluation.

Quality of analgesia evidenced by change in VAS was dose dependent and after nebulisation by 4 µg/kg fentanyl, it was equivalent to 2 µg/kg IV fentanyl. The duration of pain relief in nebulisation group was prolonged (90 min vs. 30 min).

Table 1: Demographic data of the patients

Group	Age (years) (mean±SD)	Weight (kg)	Male	Female	P value
C (n=28)	38.14±11.23	55.4±2.41	13	15	NS
NI (n=26)	36.51±8.15	56.19±1.82	15	11	
NII (n=29)	35.91±9.14	55.52±2.12	12	15	

Group C – Control (IV fentanyl 2 µg/kg); Group NI – Fentanyl nebulisation group I @ 3 µg/kg; Group NII – Fentanyl nebulisation group II @ 4 µg/kg; NS – Not significant ( $P>0.05$ ); SD – Standard deviation; IV – Intravenous

Table 2: Changes in mean VAS

Time interval (min)	Group C (n=28)	Group NI (n=26)	Group NII (n=29)	F value	P value
5	-2.90±0.568	-0.10±0.316	-0.10±0.316	4.532	0.002
10	-0.5±0.412	-0.80±0.20	-1.30±0.316	61.000	0.001
15	-0.10±0.316	-1.00±0.030	-1.90±0.316	361.000	0.001
30	-0.02±0.699	-0.10±0.316	-0.90±0.316	31.105	0.07
45	1.70±1.337	-0.00±0.000	-0.80±0.707	3.000	0.04
60	NA	-0.80±0.699	-0.40±0.26	-	-
90	NA	-0.40±0.035	-0.90±1.337	-	-
120	NA	1.50±1.080	1.60±1.265	-	-

NA – Not available; Group C – Control (IV Fentanyl 2 µg/kg); Group NI – Fentanyl nebulisation group I @ 3 µg/kg; Group NII – Fentanyl nebulisation group II @ 4 µg/kg; VAS – Visual analogue scale; IV – Intravenous

Table 3: Ramsay sedation score during study

Time interval (min)	Group C (n=28)	Group NI (n=26)	Group NII (n=29)	F value	P value
0	1.50±0.527	1.40±0.527	1.40±0.516	0.091	0.965
5	2.80±0.422	1.40±0.516	1.50±0.527	13.800	0.001
10	2.80±0.422	1.70±0.483	1.80±0.516	17.459	0.001
15	2.20±0.422	1.70±0.483	2.00±0.516	17.459	0.001
30	2.11±0.333	2.01±0.422	2.30±0.483	1.241	0.310
45	2.10±0.422	2.06±0.483	2.40±0.516	6.443	0.01
60	2.16±0.516	2.10±0.316	2.30±0.316	2.571	0.069
90	2.0±0.527	2.00±0.422	2.00±0.483	2.516	0.074
120	1.40±0.516	1.30±0.422	1.40±0.483	9.590	0.054

Group C – Control (IV fentanyl 2 µg/kg); Group NI – Fentanyl nebulisation group I @ 3 µg/kg; Group NII – Fentanyl nebulisation group II @ 4 µg/kg; IV – Intravenous

Table 4: Incidence of adverse effect in various groups

Complications	Group C (n=28)		Group NI (n=26)		Group NII (n=29)		P value
	No.	%	No.	%	No.	%	
PONV	4	13	1	4	1	4	NS
Pruritus	4	13	0	0	2	8	NS
Hypoxia	0	0	0	0	0	0	NS
Urinary retention	0	0	0	0	0	0	NS
Bradycardia	0	0	0	0	0	0	NS

PONV – Post-operative nausea and vomiting; Group C – Control (IV fentanyl 2 µg/kg); Group NI – Fentanyl nebulisation group I @ 3 µg/kg; Group NII – Fentanyl nebulisation group II @ 4 µg/kg; NS – Not significant ( $P>0.05$ )

RSS in control group reached peak at 5 min and decreased after 1 h. In Nebulisation group, it increased after 10 min in dose dependent manner but was always

less than control group during study. This finding can be attributed to slow rise in peak plasma concentration by inhalational administration of fentanyl. This correlates with the finding by previous studies that maximum serum concentration of fentanyl is reached at 13 min after intranasal administration as compared to IV administration (2-3 min).<sup>[6]</sup>

In the present study, the oxygen saturation was comparable in all the three groups and statistically non-significant ( $P > 0.05$ ). We observed stable heart rate, blood pressure, respiratory rate in nebulisation groups when compared with control group. This finding can be attributed to slow rise in peak plasma concentration by inhalational administration of fentanyl.

No major adverse effects like respiratory depression; hypoxia or bronchospasm was observed in any of the groups. This correlates with the finding by Worsley<sup>[1]</sup> and Higgins.<sup>[8]</sup> Side-effects such as pruritus, nausea and vomiting were observed in all the three groups and were dose dependent.

Overall, as a primary outcome of the study revealed a delayed onset of analgesia in patients on nebulised fentanyl in either concentration (3 or 4  $\mu\text{g}/\text{kg}$ ) compared to IV fentanyl 2  $\mu\text{g}/\text{kg}$  (10 min vs. 5 min) but the effect was prolonged (90 min vs. 30 min). The quality of analgesia with nebulised fentanyl 4  $\mu\text{g}/\text{kg}$  was found equivalent to the control group of patients with IV fentanyl 2  $\mu\text{g}/\text{kg}$ . As a secondary outcome measure the side-effects of the drug were found to be minimal in the nebulised group.

However, there are certain limitations of this study. As we were evaluating efficacy of nebulised fentanyl we have not evaluated total consumption of fentanyl in 24 h by nebulisation route considering it as sole analgesic. Further, the number of patients included in the study is small and warrants further investigation by increasing the sample size. The present study included only patients who underwent lower abdominal surgery

under spinal anaesthesia. However, the usefulness of inhaled fentanyl is limited as there are many situations such as head and neck surgery, patients with orofacial trauma, uncooperative and agitated patients where inhaled fentanyl administration is difficult/impossible.

A PubMed search revealed no systematic reviews or trials on this subject as of now. The results of this study are encouraging and we intend to explore the findings further.

## CONCLUSIONS

This trial shows that post-operatively 4  $\mu\text{g}/\text{kg}$  nebulised fentanyl produces comparable pain relief to 2  $\mu\text{g}/\text{kg}$  IV fentanyl, for a longer duration and with minimal side-effects. This study opens the door for further work on nebulisation of fentanyl as an alternative non-invasive method of analgesia.

## REFERENCES

1. Worsley MH, MacLeod AD, Brodie MJ, Asbury AJ, Clark C. Inhaled fentanyl as a method of analgesia. *Anaesthesia* 1990;45:449-51.
2. Bartfield JM, Flint RD, McErlean M, Broderick J. Nebulized fentanyl for relief of abdominal pain. *Acad Emerg Med* 2003;10:215-8.
3. Furyk JS, Grabowski WJ, Black LH. Nebulized fentanyl versus intravenous morphine in children with suspected limb fractures in the emergency department: A randomized controlled trial. *Emerg Med Australas* 2009;21:203-9.
4. Miner JR, Kletti C, Herold M, Hubbard D, Biros MH. Randomized clinical trial of nebulized fentanyl citrate versus i.v. fentanyl citrate in children presenting to the emergency department with acute pain. *Acad Emerg Med* 2007;14:895-8.
5. Chrubasik J, Geller E, Niv D, Zindler M. Morphine inhalation versus intravenous infusion in pain treatment after abdominal surgery. *Anesth Analg* 1987;66:29.
6. Kissin I. Preemptive analgesia. *Anesthesiology* 2000;93:1138-43.
7. Mather LE, Woodhouse A, Ward ME, Farr SJ, Rubsamen RA, Eltherington LG. Pulmonary administration of aerosolised fentanyl: Pharmacokinetic analysis of systemic delivery. *Br J Clin Pharmacol* 1998;46:37-43.
8. Higgins MJ, Asbury AJ, Brodie MJ. Inhaled nebulised fentanyl for postoperative analgesia. *Anaesthesia* 1991;46:973-6.

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