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A prospective randomised single blind clinical comparative evaluation of analgesia of nebulised fentanyl (4mcg/kg) with intravenous fentanyl (1mcg/kg) for post operative pain relief in abdominal surgeries

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Abstract
Aim and Objectives: To compare postoperative analgesic efficacy of nebulised fentanyl (4mcg/kg) with intravenous fentanyl (1mcg/kg) in abdominal surgeries by using VAS score and to compare the adverse effects namely Bradycardia, hypotension, respiratory depression, nausea and vomiting, pruritus and excessive sedation.
Material and Methods: Sixty patients of either sex, scheduled for elective abdominal surgeries belonging to physical status ASA class 1 and 2 were allocated into two groups of 30. Patients belonging to study group (group S) received nebulised fentanyl (4mcg/kg) and IV saline. Patients belonging to control group (group C) received intravenous fentanyl (1mcg/kg) and nebulised saline. Patients were assessed for pain by VAS, sedation by RSS, hemodynamic parameters: (heart rate, blood pressure, respiratory Rate) and adverse effects (nausea, vomiting, pruritus).
Results: Demographic profile was comparable in both the groups. The mean baseline VAS score in group C(7.7±1.55) decreased until 30 min to mean VAS of 1.2±0.71 whereas in group S(7.0±1.38) it decreased until 90 min to mean VAS of 0.37±0.56 and was both statistically and clinically significant. The differences in systolic and diastolic blood pressure were statistically significant in both the groups (group C and group S) however the difference noted was not clinically significant bradycardia was observed in one patient of group C. Nausea and vomiting was observed in 3 patients of group C and 4 patients of group S. Pruritus was observed in 4 patients of group C and 2 patients of group S.
Conclusion: Postoperatively both the drugs were effective in giving pain relief. 4 mcg/kg nebulised fentanyl produces significant lower pain scores for prolonged time as compared to 1mcg/kg intravenous fentanyl (90 mins vs 30 mins) and with minimal side effects. Thus nebulised fentanyl is an effective, safe and convenient method of analgesia.

Keywords: nebulised fentanyl, postoperative analgesia, abdominal surgeries

1. Introduction
The main essence of anaesthesia is adequate pain relief with rapid and a complete recovery with minimal side effects. Opiate analgesia may assist the anaesthesiologist in this task while providing relief for the patient. Fentanyl may be chosen over other analgesics because of its rapid onset of action (2-5mins) and high potency (~100 times potent than morphine) [1, 2] Fentanyl is generally administered intravenously and considered a gold standard for post-operative pain relief. However, the IV fentanyl is often associated with complications such as respiratory depression, bradycardia, hypotension, pruritus and nausea/vomiting. The alternative route could be pulmonary drug delivery. Nebulizers are capable of producing aerosols of fine particle size which penetrate the bronchial tree and are deposited in airways and alveoli to be drained by both the bronchial and pulmonary circulation leading to systemic absorption. A simple method of analgesia which is rapidly effective with the minimum of complex apparatus would be useful for the postoperative patient and for self administration by those suffering severe pain at home.

2. Method
Sixty patients of either sex, scheduled for elective abdominal surgeries belonging to physical status ASA class 1 and 2 were allocated into two groups of 30.

2.1 Inclusion criteria
Participants with complains of postoperative pain with VAS Score>4
Participants who will be available for assessment up to 2 hours post operatively.
Participants in age group between 18 to 45 years.
Participants willing to participate in study.
Participants belonging to physical status ASA I and ASA II.

2.2 Exclusion criteria
Participants with known sensitivity to opioids.
Parturients.
Individual suffering from asthma, rhinitis or respiratory symptoms URTI/LRTI.
Patient refusal.
Patients with chronic opiate use.

2.3 Sample size
For power of 80%, and alpha value of 0.05 at two-tailed test. Efficacy of Fentanyl was considered 100% by IV route (control group) and in nebulisation group it was taken as 75%. For this sample size was calculated as 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.

2.4 Study design

Prospective randomised single blind study

Group C (IV Fentanyl) : patients received intravenous fentanyl (1mcg/kg) and nebulised saline (4cc)

Group S (Nebulised Fentanyl): patients received nebulised fentanyl (4mcg/kg) and IV saline (4cc)

Participants were nebulised by a standard ventimask having nebulisation chamber at a constant flow rate of oxygen 8-10 l/min for 10 min.

Heart rate, Systolic BP, Diastolic BP and Respiratory rate were noted at 0, 2, 5, 10, 15, 30, 45, 60, 90 and 120 minutes.

Sedation was noted based on Ramsay sedation scale(1 - anxious/restless or both 2 - cooperative, oriented and tranquil responding to command;3 responds to commands only,4 - brisk response to stimulus; 5 - sluggish response to stimulus; 6 - no response to any stimulus)

Participants pain was noted using Visual Analogue Scale (0 - no pain, 10 - maximum imaginable pain).Participants were monitored for nausea/ vomiting,bradycardia (HR<60 beats/min or >30% fall from the baseline value),respiratory depression(respiratory rate <8), hypotension (SBP<90 mm Hg or >30% fall from the baseline value) pruritus(participant complains of itching)

2.5 Rescue Plan

If PR <50 beats/min or fall more than 30 % of baseline, Inj Atropine 0.6 mg was given bolus.

Hypotension defined as fall in SBP more than 30 % from the baseline or <90 mm Hg and treated with infusion of crystalloid solution and inj. Mephentermine 6 mg in incremental doses.Pruritus was treated with inj pheniramine maleate 45 mg IV.Nausea and vomiting was treated by inj. Ondansetron 4mg iv.Rescue analgesic- inj. diclofenac 75 mg IV was given as rescue analgesic when patient requested for analgesia. Respiratory depression was treated with oxygen using bag mask ventilation.

3. Results and Discussion

Statistical Analysis was done using SPSS 24.0 version. Unpaired and paired t-test and general linear model of repetitive measurements were used for quantitative nominal data (mean +/-) whereas categorical data was compared using Fischer exact test. $p<0.05$ was considered significant.

3.1 Demographic Data

Table 1: Age distribution (years)

Age groups (years)	Group C [IV fentanyl (1mcg/kg)]		Group S [nebulised fentanyl (4mcg/kg)]	
	Number	Percentage	Number	Percentage
18-30	13	43.3	11	36.6
31-40	14	46.6	16	53.3
41-45	03	10	03	10
Total	30	100	30	100

Table 2: Sex distribution

Sex	Group C		Group S	
	Number	Percentage	Number	Percentage
Male	13	43.3	14	46.6
Female	17	56.6	16	53.3
Total	30	100	30	100

Table 3: Weight distribution (kg)

Sex	Group C		Group S	
	Number	Percentage	Number	Percentage
Male	13	43.3	14	46.6
Female	17	56.6	16	53.3
Total	30	100	30	100

Demographic data like age, sex, weight were comparable in all the three groups (P>0.05).

3.2 Heart Rate

Table 4: Hemodynamic parameters - Heart rate (beats/min)

	Group	Mean	Std. Deviation
Base	Group C	91.00	7.760
	Group S	94.00	5.484
2 minutes	Group C	98.00	5.106
	Group S	98.00	5.106
5 minutes	Group C	94.00	5.484
	Group S	98.00	5.106
10 minutes	Group C	86.00	6.873
	Group S	94.00	5.484
15 minutes	Group C	84.00	6.091
	Group S	90.00	7.965
30 minutes	Group C	84.10	5.410
	Group S	86.00	6.873
45 minutes	Group C	86.00	6.873

	Group S	84.00	6.091
60 minutes	Group C	88.00	6.281
	Group S	84.00	6.091
90 minutes	Group C	94.00	5.484
	Group S	88.00	6.281
120 minutes	Group C	96.07	4.394
	Group S	90.00	7.965

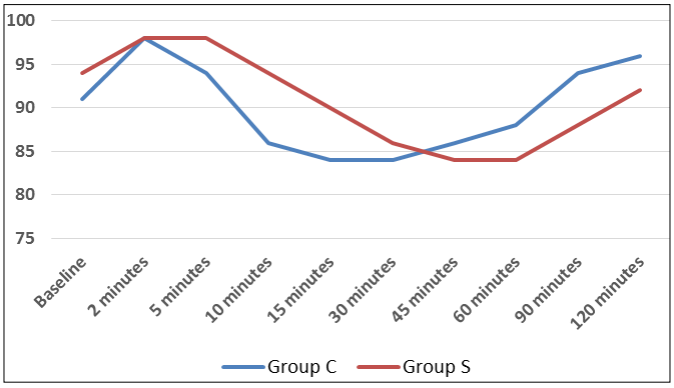

Fig 1: Hemodynamic parameters - Heart rate (beats/min)

After applying General Linear Model for repeated measures in SPSS 24.0, there was no significant variation in Heart rate between both groups. P= 0.164 which is more than 0.05.The mean baseline heart rate of the group C and group S was 91±7.76 and 94±5.48 respectively and the difference observed in both the groups was statistically non-significant. The change observed in heart rate in both the groups over the period of time was almost same and the difference observed was statistically non-significant. Singh *et al.* [3], Saranya *et al.* [4], and Ershad *et al.* [5] reported stable heart rate in nebulisation group when compared with iv group. This finding can be attributed to slow rise in peak plasma concentration by inhalational administration of fentanyl.Our findings concur with the findings of Singh *et al.* [3], Saranya *et al.* [4], and Ershad *et al.* [5]

3.3 Blood Pressure

Table 5: Mean systolic blood pressure (mm hg)

	Group	Mean	Std. Deviation
Base	Group C	132.00	3.601
	Group S	130.00	9.584
2 minutes	Group C	130.00	9.584
	Group S	132.00	3.601
5 minutes	Group C	128.00	4.698
	Group S	130.00	9.584
10 minutes	Group C	124.00	4.785
	Group S	130.00	9.584
15 minutes	Group C	122.00	10.954
	Group S	132.00	3.601
30 minutes	Group C	124.00	4.785
	Group S	124.00	4.727
45 minutes	Group C	124.00	4.727
	Group S	128.00	4.698
60 minutes	Group C	128.00	4.698
	Group S	126.00	5.433
90 minutes	Group C	132.00	3.601
	Group S	132.00	3.601
120 minutes	Group C	134.00	8.694
	Group S	134.00	8.694

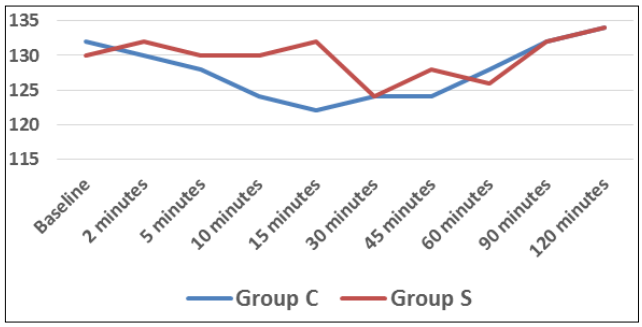

Fig 2: Mean systolic blood pressure (mm hg)

After applying General Linear Model for repeated measures in SPSS 24.0, there was a significant variation in systolic BP between both groups. P= 0.004 which is less than 0.05. However the difference noted in systolic BP was not clinically significant.

Table 6: Mean diastolic blood pressure (mm hg)

	Group	Mean	Std. Deviation
Base	Group C	82.00	2.573
	Group S	82.00	2.573
2 minutes	Group C	82.00	2.573
	Group S	84.00	3.063
5 minutes	Group C	78.00	4.955
	Group S	84.00	3.063
10 minutes	Group C	78.00	4.955
	Group S	82.00	2.573
15 minutes	Group C	74.00	3.787
	Group S	82.00	2.573
30 minutes	Group C	72.00	3.824
	Group S	74.00	3.787
45 minutes	Group C	72.00	3.824
	Group S	72.00	3.824
60 minutes	Group C	72.00	3.824
	Group S	74.00	3.787
90 minutes	Group C	76.00	2.971
	Group S	78.00	4.955
120 minutes	Group C	80.00	3.444
	Group S	82.00	2.573

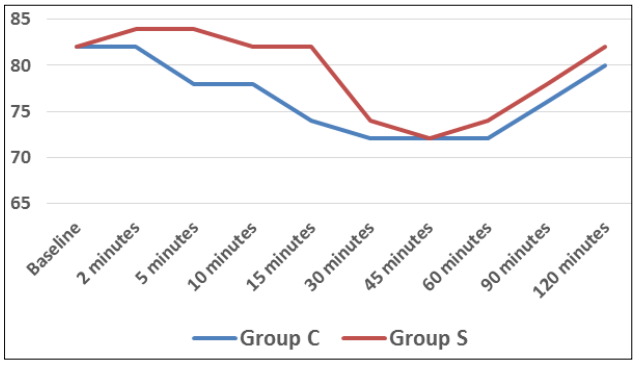

Fig 3: Mean diastolic blood pressure (mm hg)

After applying General Linear Model for repeated measures in SPSS 24.0, there was a significant variation in Diastolic BP between both groups. P= 0.000 which is less than 0.05. However the difference noted in Diastolic BP was not clinically significant.

The mean baseline systolic BP in group C was 132±3.60mmhg. The mean baseline systolic BP in group S was 130±9.58mmhg. The difference observed in both the groups at baseline was statistically non-significant.

The mean baseline diastolic BP in group C was 82±2.57mmhg. The mean baseline diastolic BP in group S was 82±2.57mmhg. The difference observed in both the groups at baseline was statistically non-significant.

In the present study, the systolic and diastolic blood pressure in both the groups (group C and group S) showed significant variation ($P > 0.05$) with lower values of systolic and diastolic BP in Group C (iv fentanyl). However the differences observed were not clinically significant, with differences in SBP and DBP approximately around 10 mm hg.

Singh *et al.* [3], Saranya *et al.* [4], and Ershad *et al.* [5] in contrast reported stable SBP and DBP in nebulisation group when compared with iv group. This finding can be attributed to slow rise in peak plasma concentration by inhalational administration of fentanyl.

3.4 Ramsay sedation score

Table 7: Ramsay sedation score

	Group	Mean	Std. Deviation
Base	Group C	1.40	0.50
	Group S	1.30	0.47
2 minutes	Group C	1.57	0.50
	Group S	1.37	0.48
5 minutes	Group C	2.87	0.35
	Group S	1.63	0.48
10 minutes	Group C	2.90	0.55
	Group S	1.87	0.54
15 minutes	Group C	2.23	0.43
	Group S	2.17	0.54
30 minutes	Group C	2.03	0.49
	Group S	2.33	0.55
45 minutes	Group C	2.13	0.57
	Group S	2.40	0.63
60 minutes	Group C	2.10	0.61
	Group S	2.43	0.51
90 minutes	Group C	2.00	0.69
	Group S	2.17	0.52
120 minutes	Group C	1.23	0.43
	Group S	1.47	0.51

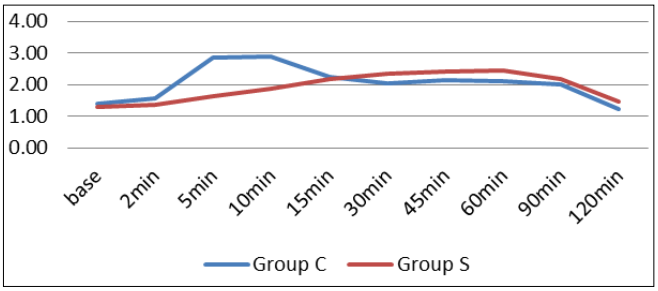

Fig 4: Ramsay sedation score

Mean Ramsay sedation scores were transformed into ranks and analyzed in General Linear Model for repeated measures in SPSS 24.0, P= 0.015 which is less than 0.05 and hence there was a significant variation in RSS between both groups.

It was seen that the mean baseline Ramsay sedation score in group C was 1.40±0.50 and in group S was 1.30±0.47. The difference observed in both the baseline scores was statistically non-significant. It was observed that the mean sedation score was rising after administration of drug and reached to the peak of 2.90±0.55 in group C at 10min. In group S mean sedation score reached to peak of 2.43±0.51 after 60min of administration. The difference observed in the sedation score was found to be statistically significant (P> 0.05) as analyzed by GLM of repetitive measurements in SPSS software. Mean sedation scores in group C were higher than that of Group S until 15min. After 15min mean sedation scores in Group S stayed higher, This finding can be attributed due to the 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) [55, 57, 58]. However the difference noted was not clinically significant and the mean sedation scores in both the groups were less than 5.Singh *et al.* [3], observed that in groups NI(3mcg/kg nebulized fentanyl) and NII(4mcg/kg nebulized fentanyl), there was a slow rise in the sedation score but it was always less than in group C (IV fentanyl group).Saranya *et al.* [4] found that in control group (Group C), sedation score reached to the peak at 5 minutes after the administration of the drug. However, in the nebulisation group (Group N), it was found that sedation score increased after 10 minutes of administration.In the study conducted by Ershad *et al.* [5], the sedation score in group A (IV fentanyl group) was maximum at 5 min whereas in group B (nebulised fentanyl group), there was a slow rise in the sedation score but it was always less than in group A. Our findings concur with the findings of Singh *et al.* [3], Saranya *et al.* [4] and Ershad *et al.* [5]

3.5 Visual analogue score

Table 8: Mean visual analogue score

Time interval	Group	Mean	Std. Deviation
Base	Group C	7.7	1.55
	Group S	7.0	1.38
2 minutes	Group C	7.1	1.61
	Group S	6.2	1.49
5 minutes	Group C	6.4	1.85
	Group S	5.8	1.85
10 minutes	Group C	4.2	1.25
	Group S	3.57	0.68
15 minutes	Group C	2.6	0.56
	Group S	3.10	0.71
30 minutes	Group C	1.2	0.71
	Group S	2.77	0.63
45 minutes	Group C	3.2	0.57
	Group S	1.17	0.70
60 minutes	Group C	2.8	0.66
	Group S	0.73	0.69
90 minutes	Group C	3.1	0.61
	Group S	0.37	0.56
120 minutes	Group C	2.1	0.78
	Group S	1.67	0.71

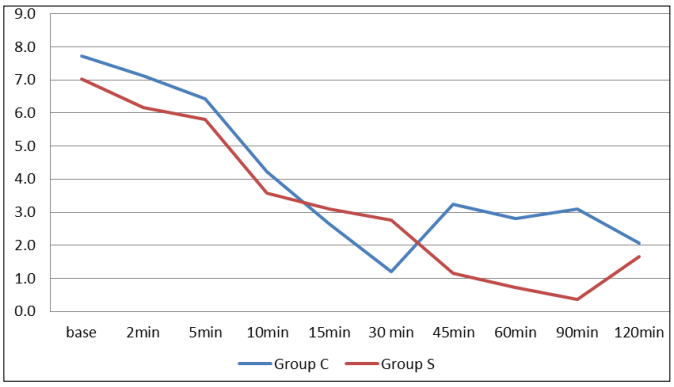

Fig 5: Mean visual analogue score

Mean Visual Analogue Scores were transformed into ranks and analyzed in General Linear Model for repeated measures in SPSS 24.0, P= 0.000 which is less than 0.05 and hence there was a significant variation in VAS between both groups. It was seen that mean visual analogue score at base in group C was 7.7±1.55 whereas in group S it was 7.0±1.38 and the difference observed was statistically non-significant. Pain score showed significant decrease compared to the reading before drug administration in both the groups. The pain score in group C decreased until 30min to mean VAS of 1.2±0.71 whereas in group S pain score decreased until 90min to mean VAS of 0.37±0.56 after administration. The difference observed was statistically significant as analyzed by GLM of repetitive measurements in SPSS software. This correlates to the finding by previous studies that nebulized fentanyl produces prolonged analgesia as compared with intravenous fentanyl.Bartfield *et al.* [6], reported that the group receiving intravenous fentanyl (group I) had a greater reduction in mean pain scores; however, this difference was not significant by 30 minutes following fentanyl administration. At 30 minutes the mean change in pain score for group I (IV fentanyl group) was 25 mm, compared with 16 mm for group II (nebulised fentanyl group). At 15 minutes the mean change in pain score for group I was 25 mm, compared with 10 mm for group II. Twelve of the 24 (50%) group I subjects received rescue medication at 30 minutes, compared with 18 of 26 (69%) group II subjects (p >0.25).Singh *et al.* [3] observed that there was statistically significant mean VAS change starting at 5 min and continued until 15 min ($P < 0.005$). VAS decreased until 30 min in group C (IV fentanyl group) and until 90 min in groups NII (nebulised fentanyl group).In the study by Ershad *et al.* [5], statistically significant mean VAS change started at 5 min and continued until 15 min (P < 0.005). VAS decreased until 30 min in group A (IV fentanyl group) and until 90 min in group B (nebulised fentanyl group).Saranya *et al.* [4] in his study, 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).Our finding concur with the findings of Bartfield *et al.* [6], Singh *et al.* [3], Ershad *et al.* [5] and Saranya *et al.* [4].

3.6 Adverse Effects

Statistical analysis was done using Fischer exact test. P > 0.05 for all adverse effects and hence statistically non-significant.3 incidences of PONV were seen in group C as compared to 4 incidences in group S however the differences were not statistically significant.4 incidences of PONV were seen in group C as compared to 2 incidences in group S however the differences were not statistically significant.

Table 9: Incidence of adverse effects

Complications	Group C	Group S	p value
Hypotension	0	0	1.00 (NS)
Bradycardia	1	0	1.00 (NS)
PONV	3	4	1.00 (NS)
Pruritus	4	2	0.67 (NS)
Respiratory Depression (RR <8)	0	0	1.00 (NS)

Ershad *et al.* [5] reported that adverse effects in group B (nebulised fentanyl group) were less compared with the group A (IV fentanyl group) though statistically insignificant. Similar findings were also reported by Bartfield *et al.* [6], Singh *et al.* [3], Saranya *et al.* [4], Higgins *et al.* [7] and Worsley *et al.* [8] in their studies.

4. Conclusion

Our trial showed that post operatively both the drugs were effective in giving pain relief. 4 mcg/kg nebulised fentanyl produces significant lower pain scores for prolonged time as compared to 1 mcg/kg intravenous fentanyl (90 mins vs 30 mins) and with minimal side effects. Thus the nebulised fentanyl is an effective, safe and convenient method of analgesia.

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