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Comparision of Effects of Fentanyl and Intravenous Paracetamol on Consumption of Sevoflurane

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Abstract

Aims: The study was designed to compare the effect of IVFentanyl vs. IV Paracetamol on consumption of Sevoflurane and the recovery characteristics. *Plan of study:* Patients scheduled for elective surgeries under general Anaesthesia are randomly allocated with 50 patients in each group. Group- F received Fentanyl 1mcg/kg per min as bolus 5min before infusion immediately after intubation. Group- P received Paracetamol 1gm in 100ml for a period of 15min and twenty five minutes before intubation. Intra-operatively Sevoflurane concentration was titrated to maintain entropy value of 40-60. Total volume of Sevoflurane consumed is obtained from GE/Datex-Omeda S/5 advance monitor and average Sevoflurane consumed in ml/hr is calculated.*Results:* Consumption of Sevoflurane in Group- F was 16.01 ± 0.95ml/hr as compared to 16.9 ± 2.2 ml/hr in Group- P which was statistically significant. Post extubation at the end of fifth minute all patients in Group- P attained score of 12 as compared to only 56% patients of Group- F and it was is statistically significant (p <0.001). *Conclusion:* Consumption of Sevoflurane & post-operative pain was less in Fentanyl group when compared to paracetamol group. However recovery characteristics are better in paracetamol group.

Keywords: IV Paracetamol, IV Fentanyl, Consumption of Sevoflurane, Entropy.

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Introduction

A patient hypnotic state can be evaluated in real time using several devices that quantify the EEG. Entropy module based upon spectral entropy describes the irregularity, complexity or unpredictability of a signal. Monitoring anaesthetic depth makes it possible to administer appropriate dose of anaesthetics and prevent anaesthetic awareness, side effects of over dose, economic and environmental waste. Anaesthetic management using proper volatile anaesthetic administration is equally important as maintaining patient's vital signs[2]. Demonstrations have shown that intravenous paracetamol is associated with rapid, predictable analgesia in perioperative period.

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Entropy is considered to be more accurate and reliable indicator of the hypnotic effect of anaesthetics and sedative drugs.[3] The entropy module generates state entropy (SE) and response entropy (RE).The SE frequency is in the range of 0.8-32 Hz of the raw EEG signal and RE frequency is in the range of 0.8-47 Hz.[4]

Intraoperative analgesia is an integral component of balanced anaesthesia technique. Opioids remain the agent of choice for severe pain; however this class of analgesics is associated with dose dependent adverse effects and untoward post-operative outcomes.[5]

It was demonstrated that there is profound synergism for both analgesia and sedation between Opioids and volatile anesthetics.[6] Fentanyl and its congeners are being used for managing the analgesic component and were shown to reduce the MAC of Sevoflurane.[7]

When multiple intravenous doses of Fentanyl are administered or when there is continuous infusion of the drug, the plasma concentration of Fentanyl does not decrease rapidly & the duration of analgesia as well as depression of ventilation may be prolonged.[8]

Paracetamol, a non-opioid agent by virtue of its central cyclooxgenase inhibition and its indirect influence on serotonergic system is found to be an effective analgesic.[9] It has a good safety profile & easily crosses the blood brain barrier & thus produces analgesia.[10] Various authors have studied the effect of Paracetamol on intraoperative and postoperative analgesic consumption and found to have an opioid sparing effect.[11] Studies are scarce as to the effect of intravenous Paracetamol on consumption of Sevoflurane and recovery characteristics. This clinical study is designed and aimed to compare the effect of intravenous Paracetamol and Fentanyl on consumption of sevoflurane and recovery characteristics using Entropy monitored general anaesthesia.

Materials and Methods

After institutional ethical committee approval, written informed consent was taken from patients belonging to physical status ASA I & II.The study included 100 patients. They were randomly allocated into 2 equal groups. Patients of age group 20-50yrs were selected for the study undergoing general anaesthesia.Preanaesthetic evaluation and investigations were done of all the patients participating in study. Patients with anticipated difficult intubation, who are already receiving Opioid & analgesics, patients whose body weight <70% or >130% of ideal body weight were excluded from the study.

Sample size was calculated based on previous studies. Keeping confidence limit at 15%, and power of study being 80%, minimum sample size required to detect a 15% difference in Sevoflurane concentration consumption was 72. To overcome errors and non-participation, 100 patients were selected and randomly divided into two groups with 50 patients in each group.

Group- F: Received Fentanyl 1mcg/kg body weight IV bolus 5min before the intubation, (Fentanyl bolus was given to obtain adequate analgesic concentration in perioperative period till the infusion is started) followed by 0.02mcg/ kg per min infusion of Fentanyl immediately after intubation.

Group- P: Received IV Paracetamol 1gm in 100ml over 15min, twenty five minutes before the plan of induction & intubation.

After shifting the patient to operating room, IV access was obtained on the forearm with 18G IV cannula and ringer lactate infusion started. Premedication was done with Midazolam 1mg IV, Glycopyrrolate 0.2mg, Tramadol 50mg IV and was preoxygenated with 100% O_2 for 3 min. Induction was done with IV Propofol 2mg/kg and intubation was facilitated with IV Atracurium 0.5mg/kg, controlled ventilation with 6liters of fresh gas flow N_2O:O_2 (60:40).

After intubation, Sevoflurane was set and its concentration was titrated every 5min by 0.5 volume% to maintain SE value 40-60. (The gradient between SE & RE was maintained in the range of 5-10). Once the inspired and expired concentrations of Sevoflurane are equal or ±0.2%, the fresh gas flow was reduced to 2 litres/min. Sevoflurane was switched off at the time of beginning of skin stapling. At the end of skin closure, fresh gas flow was increased to 6 litres/min with 100% oxygen.Each patient was monitored for electrocardiography, oxygen saturation, Et Sevoflurane, MAC, non-invasive blood pressure, EtCo2, train of four (TOF), State Entropy (SE) & Response Entropy (RE) .

Both the groups received sevoflurane after intubation.Neuromuscular blockade was reversed with Neostigmine 0.05mg/kg and Glycopyrolate 0.01mg/kg. When TOF count was 4, Sevoflurane starting and cutoff time were noted. Total volume of Sevoflurane consumed for each case was obtained from GE/Datex-Omeda S/5 avance monitor and Sevoflurane consumed in ml/hr was calculated. After extubation, the anaesthesia monitoring

was continued till 10min. Recovery status was ascertained by fast-track scoring system.

Statistical analysis

Data was analysed using SPSS V18 software. *p*- Value < 0.05 was considered forstatistical significance.Descriptive statistics of $ETCO_2$, FiSevo, MAC, and duration of surgery were noted. Sevoflurane consumption & haemodynamic variables were analysed and presented with mean and standard deviation. Independent t-test was used to compare the average $ETCO_2$, Fi Sevo, MAC, Duration of surgery, Sevoflurane consumption and haemodynamic variables were compared at different time. Chi-square test was used to compare the level of consciousness score, physical activity score, respiratory stability, oxygen saturation score & pain assessment score between the groups.

Results

The patients' demographics with respect to age, height, weight, gender distribution, ASA grading and duration of surgery were comparable between the groups. Mac sevoflurane required for anaesthetic depth in Group-P was significantly higher than Group-F. Sevoflurane consumption was significantly higher when compared to Group- F (*p* value- 0.053). Heart rate, SBP, DBP and MAP were significantly higher in Group- P when compared to Group- F.

Recovery characteristics as assessed by Fast Track Scoring System, level of consciousness, physical activity, oxygen saturation status, and emetic symptoms were comparable in both the groups. Haemodynamic parameters were found to be high at 3rd and 4th minute in Group- P. The immediate pain score was high in Group- P as compared to Group- F. At the end of fifth minute 100% in Group- P attained score of 12 as compared to 56% in Group- F and was statistically significant ($p < 0.001$) and at the end of 8th minute, Group- F attained score of 12 (Tables 1-12 and Fig. 1,2).

Table 1. Demographic data

Basic variables	Group- F	Group- P	*p*- value
Age in years	40 ± 7.3	39 ± 8.7	0.67
Height in cm	157.60 ± 3.84	156.80 ± 3.06	0.78
Weight in kg	57.8 ± 6.9	60 ± 5.1	0.58
Duration of Surgery	85.7 ± 16	91.2 ± 15	0.09

Table 2. Comparison of MAC and duration of Sevoflurane usage

	Group- F	Group- P	*p*- Value
MAC	1.28 ± 0.08	1.38 ± 0.07	0.000*
Duration of Sevoflurane Usage	85 ± 17min	89 ± 17.5min	0.159

Table 3. Comparison of Sevoflurane consumption

	Group- F	Group- P	*p*- value
Sevoflurane Consumption ml	22.3 ± 3.8	24.06 ± 5.04	0.053
Sevoflurane ml/ hour	16.01 ± 0.95	16.9 ± 2.2	0.012*

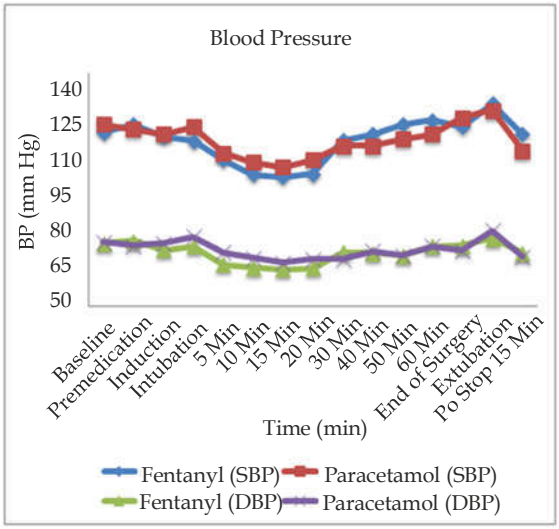

Fig. 1: Comparison of Systolic Blood pressure between the groups

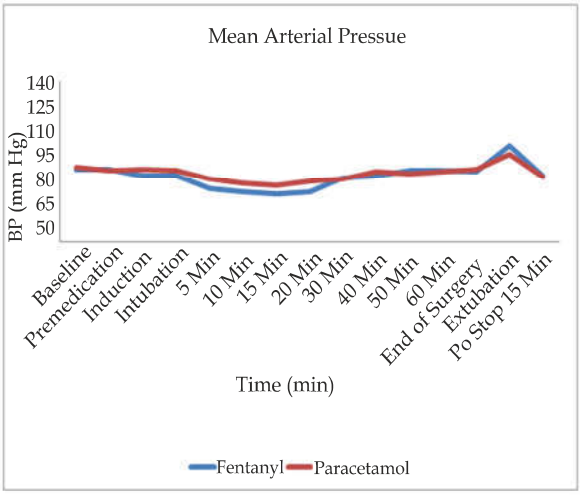

Fig. 2: Comparison of Mean Arterial Pressure between the groups

Table 4: Recovery characteristics assessed by Fast track criteria

Parameters	Description	Score
Level of consciousness	Awake and oriented	2
	Arousable with minimal stimulation	1
	Response to tactile stimulation	0
Physical activity	Able to move all extremities on command	2
	Some weakness in movement of extremities	1
	Unable to voluntarily move extremities	0
Hemodynamic stability	Blood pleasure <15% of base line MAP value	2
	Blood pleasure 15% - 30% of base line MAP value	1
	Blood pleasure >30% of base line MAP value	0
Respiratory stability	Able to breathe deeply	2
	Tachypnea with good coughs	1
	Dyspnea with weak coughs	0
Oxygen saturation status	Maintain value >90% on room air	2
	Requires supplemental oxygen (nasal prongs)	1
	Saturation <90% with supplemental oxygen	0
Post-operative pain assessment	None of Mild discomfort	2
	Moderate to severe pain controlled with IV analgesics	1
	Persistent severe pain	0
Post-operative emetic symptom	None or mild nausea with no active vomiting	2
	Transient vomiting or retching	1
	Persistent moderate to severe nausea and vomiting	0
	Total score	14

[A minimal score of 12 is taken for complete recovery. Recovery time is assessed at 1min interval and is calculated accordingly for each case]

Table 5: Comparison of level of consciousness

Level of consciousness at		0	1	2	*p* value
1 min	F	2	32	26	0.89
	P	2	24	24	
2 min	F	2	32	16	0.63
	P	0	24	26	
3 min	F	2	18	30	0.01
	P	0	4	46	
4 min	F	2	4	46	<0.001
	P	0	0	50	
5min	F	1	4	35	<0.001
	P	0	0	50	
6 min	F	0	3	47	0.242
	P	0	0	50	
7 min	F	0	2	48	0.495
	P	0	0	50	
8 min	F	0	2	48	0.495
	P	0	0	50	

[Level of consciousness and Score: Awake and oriented =2; Arousable with minimal stimulation=1 ;Response to tactile stimulation= 0]

Table 6: Comparison of Physical activity

Physical activity at		0	1	2	*p* Value
1 min	F	0	41	9	0.624
	P	0	38	12	
2 min	F	0	41	9	0.241
	P	0	35	15	
3 min	F	0	37	13	0.284
	P	0	41	19	
4 min	F	0	31	29	0.204
	P	0	21	34	
5 min	F	0	2	48	0.287
	P	0	0	50	
6 min	F	0	0	50	--
	P	0	0	50	
7 min	F	0	0	50	--
	P	0	0	50	
8 min	F	0	0	50	--
	P	0	0	50	

[Physical activity and score: Able to move all extremities on command- 2; Weaknessin movement of extremities- 1;Unable to voluntarily move extremities-0]

Table 7: Haemodynamic stability score

Haemodynamic Stability at		0	1	2	*p* value
1 min	F	0	50	0	0.117
	P	4	46	0	
2 min	F	0	49	1	0.60
	P	3	47	0	
3 min	F	0	28	22	0.001
	P	0	44	6	
4 min	F	0	27	23	0.001
	P	0	42	8	
5 min	F	0	0	50	--
	P	0	0	50	
6 min	F	0	0	50	--
	P	0	0	50	
7 min	F	0	0	50	--
	P	0	0	50	
8 min	F	0	0	50	--
	P	0	0	50	

[Blood pressure: <15% of base line MAP value -2; Blood pressure: 15% - 30% of base line MAP value - 1;Blood pressure>30% of base line MAP value 0]

Table 8: Comparison of Respiratory stability

Respiratory Stability at		0	1	2	*p* value
1 min	F	0	47	3	<0.001
	P	0	26	24	
2 min	F	0	47	3	<0.001
	P	0	26	24	
3 min	F	0	46	4	<0.001
	P	0	25	25	
4min	F	0	41	9	<0.001
	P	0	16	34	
5 min	F	0	17	33	<0.001
	P	0	0	50	
6 min	F	0	4	46	0.041
	P	0	0	50	
7min	F	0	0	50	--
	P	0	0	50	
8 min	F	0	0	50	--
	P	0	0	50	

[Respiratory stability score: Able to breathe deeply- 2; Tachypnea with good coughs- 1; Dyspneic with weak coughs- 0]

Table 9: Oxygen saturation status score

Oxygen Saturation status at		0	1	2	*p* value
1 min	F	0	2	48	0.157
	P	0	0	50	
2 min	F	0	2	48	0.157
	P	0	0	50	
3 min	F	0	2	48	0.157
	P	0	0	50	
4 min	F	0	2	48	0.157
	P	0	0	50	
5 min	F	0	0	50	--
	P	0	0	50	
6 min	F	0	0	50	--
	P	0	0	50	
7 min	F	0	0	50	--
	P	0	0	50	
8 min	F	0	0	50	--
	P	0	0	50	

[Maintain value >90% on room air - 2;Requires supplemental oxygen (nasal prongs) - 1; Saturation <90% with supplemental oxygen - 0

Table 10: Comparison of Pain assessment

Pain assessment at		0	1	2	*p* value
1 min	F	3	41	6	0.02
	P	13	37	0	
2 min	F	3	41	6	0.02
	P	13	37	0	
3 min	F	3	41	6	0.02
	P	13	37	0	
4 min	F	1	40	9	0.02
	P	10	36	4	
5 min	F	0	25	25	0.23
	P	3	27	20	
6 min	F	0	2	48	0.143
	P	3	2	45	
7 min	F	0	2	48	0.181
	P	3	0	47	
8 min	F	0	2	48	0.081
	P	3	0	47	

[Pain assessment score: None of Mild discomfort- 2, Moderate to severe pain controlled with IV analgesics- 1; Persistent severe pain- 0]

Table 11: Comparison of Post-operative emetic symptoms

Post-operative EmeticSymptoms at		0	1	2	*p* value
1 min	F	0	6	44	0.293
	P	0	3	47	
2 min	F	0	5	45	0.23
	P	0	0	50	
3 min	F	0	5	45	0.23
	P	0	0	50	
4 min	F	0	5	45	0.23
	P	0	0	50	
5 min	F	0	1	49	0.32
	P	0	0	50	
6 min	F	0	1	49	0.32
	P	0	0	50	
7 min	F	0	0	50	--
	P	0	0	50	
8 min	F	0	0	50	--
	P	0	0	50	

Table 12: Comparison of Recovery status score

Time(minute)	Paracetamol > 12No of pts (%)	Fentanyl >12 No of pts (%)	*p* value
1	2 (4.0)	0 (0.0)	0.153
2	3 (6.0)	0 (0.0)	0.079
3	11 (22.0)	2 (4.0)	0.007
4	27 (54.0)	11 (22.0)	0.001
5	50 (100.0)	28 (56.0)	<0.001
6	50 (100.0)	39 (78.0)	<0.001
7	50 (100.0)	45 (90.0)	0.022
8	50 (100.0)	50 (100.0)	1.0

Discussion

Studies have shown that fentanyl reduces MAC of sevofluraneand its consumption[19] along with opioid related side effects[5].Clinical studies have found that 1gm paracetamol employed alone is as effective as 30 mg Ketorolac, 75mg Diclofenac or 10 mg morphine with a greater safety profile[9]. Preoperatively administered intravenous paracetamol 1gm has no negative effects on intraoperative or postoperative haemodynamic parameters and ensures effective analgesia during post operative period, increases patient's satisfaction by reducing postoperative opioid consumption there by reducing the length of hospital stay[9].

In our study we considered analgesic dose of Fentanyl 0.02µg/kg/min to compare analgesic component of Paracetamol and its effect on consumption of Sevoflurane.Dose to peak effect of IV Paracetamol 1gm was found to be 20min as quoted in the study by CD Osier[15], and dose to peak effect of Fentanyl was found to be 3.6 min as shown in study by Steven Shafer[16].

O Ibreheim et al. in their study compared recovery status and Sevoflurane consumption between BIS and conventional group, where patients were induced with Propofol 1.5-2 mg/kg Fentanyl 2µg/kg and succynil choline 1-1.5 mg/ kg with Sevoflurane for maintenance with 2 litre of FGF found the consumption of Sevoflurane per hour was 15.66 ± 4.04 ml liquid which is found concurrent with our study[12]

Airbanet al have compared the use of Paracetamol on its opioid sparing effects and found to be effective when compared to placebo group.[13] Sussansoltini in their study have shown that preoperative rectal Paracetamol reduces Propofol consumption and postoperative pain in infertile women undergoing oocyte retrieval for in vitro fertilization treatment[19]. J Benito et al have demonstrated that Paracetamol and Remifentanil produced a maximum degree of MAC reduction (p = 0.002) of Sevoflurane in anesthetized rats which was clinically and statistically highly significant.[14] Human studies are scarce and we have attempted to compare effect of paracetamol on Sevoflurane consumption. MAC Sevoflurane in Paracetamol group 1.38 ± 0.07 is significantly higher than Fentanyl group1.28 ± 0.08 ($p < 0.005$).

Sevoflurane consumption in our study was 16.01 ± 2.28 ml/hour in Fentanyl groupand in Paracetamol group is 16.9 ± 2.2 ml/hour. Hence Sevoflurane consumption in paracetamol group was significantly higher than Fentanyl group (p value < 0.012). Thus the reduction of consumption of sevoflurane in paracetamol group is less compared to fentanyl group.

Recovery characteristics: Postoperative recovery characteristics among both the groups were assessed by fast track scoring system.In our study we found that at 4th and 5th minute 4- 5 patients were arousable to minimal stimulation in Group- F when compared to none in Group- P where all the patients were awake and oriented and statistically significant.

Physical activity score was comparable in both the groups. Haemodynamicaly both the groups were comparable, except at 3rd (44) and 4th (42) minute in Group- P where there was significant rise blood pressure in Group- Pas compared to patients in Group- F (28) and (27) & p value was < 0.001). In our study, we found that at the end of 1st and 2nd min 47 pts were tachypneic in Group- F and 26 in Group- P. Similarly at the end of 3rd minute 46 pts in Group- F, 25 pts in Group- P at 4th min 41 in Group- F and 16 in Group- P, at 5th min 4 in group F and 0 in

Group- P werefound statistically significant. At the end of 6th minute most of the patients were able to breathe deeply without discomfort and was found statistically in significant. Oxygen saturation was maintained > 90% in both the groups.

In our study, 16 patients experienced persistent pain. Majority of them were from Group- P (13), and as compared to Group- F (3pts). Seventy eight patients experienced moderate pain which was relieved by IV analgesics. Among them 41 patients were belonged to Group- P and 37 from Group- F. It was found to be statistically significant when compared to Group F (p value < 0.02). In Group-F transient retching was present in 6 patients as compared to 3 in Group P and found statistically insignificant.

We found at the end of 5th minute, all patients of Paracetamol group attained score of 12 whereas 56% of patients of Fentanyl group attained score 12 but at the end of 8th minute all patients of Group-F attained at score of 12, as assessed by fast track criteria. Hence recovery was better and faster in Paracetamol group than Fentanyl group. SBP in both the groups were comparable. During intubation, there was significant rise in SBP in Group-P (127 ± 7.6) when compared to group F(121 ± 10). (p value < 0.001). MAP in both the groups were comparable except during intubation where in Group- P (90 ± 10.27), there was significant rise in MAP when compared to Group- F (87 ± 7.8) was found significant (p value <0.001). O ibhraiem et al. in their study on post-operative recovery and Sevoflurane consumption determined that the time to wakening and extubation was 6.8 ± 2.4 min.[12] Brestin etal in their study Sevoflurane--nitrous oxide anaesthesia supplemented with remifentanil:effect on recovery and cognitive function determined that eye opening of patient was 6.5 min and patients were oriented by the end of 8.3 min.[18] In our study we found that by the end of 6th minute most of the patients were awake, oriented and moving all the four limbs. These observations were found concurrent with the above studies.

Conclusion

Consumption of Sevoflurane in Fentanyl group was less. In Fentanyl group, patientswere haemodynamically stable intraoperatively and experienced less pain postoperatively when compared to Paracetamol group. Recovery characteristics were better in Paracetamol group as compared to Fentanyl group.

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