ORIGINAL ARTICLE

COMPARISON OF ORAL TRANSMUCOSAL FENTANYL CITRATE AND INTRAMUSCULAR FENTANYL CITRATE AS PREMEDICATION FOR GENERAL ANAESTHESIA

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ABSTRACT: Just an imagination of getting a needle prick is frightening not only for children but also for most of the adults. Level of anxiety is generally very high in the preoperative period, and the aim of the premedication is to allay the anxiety. Premedication drugs are most commonly given parenterally and the needle phobia acts as a trigger for anxiety even though transiently. In our study 40 patients were randomized into two groups and one group received 200 microgram of trans mucosal Fentanyl and the other group received 100 microgram of Intramuscular Fentanyl (equipotent doses) as premedication and from the study we could conclude that trans mucosal Fentanyl was equally efficacious as intramuscular Fentanyl with no transient raise of pulse rate or blood pressure following administration of drug by this route.
KEYWORDS: General anaesthesia, Transmucosal Fentanyl, needle phobia, premedication.

INTRODUCTION: Anxiety is very common in the preoperative period, and perfect documentation for the prevalence is not found. Some studies have shown prevalence of anxiety in the patients undergoing elective surgery can be as high as 80%.[1-4] Anxious patients respond to anaesthetic exposure in different way than those patients who are non-anxious. Because of anxiety induced vasoconstriction, securing venous lines will be difficult and may also necessitate multiple attempts for the same.[5] Anxious patients add on to the problems together to the pathology for which they are undergoing surgery by the fact that they require larger dose of anaesthetic agent and have also problems during recovery from anaesthesia.[6,7] Because of these reasons anxiolysis has become very important part of premedication. Unfortunately most of the pre medications are given parenterally and hence requires a needle poke. The act of administration of the premedication hence carries a trigger for anxiety even though very transiently. Hence our study was designed to use the non-parenteral drug for premedication than the conventional intramuscular route.

METHODOLOGY: After obtaining institutional ethical committee approval for the study, study was aimed to compare the Oral Trans mucosal route of Fentanyl administration with Intra-muscular route of Fentanyl administration for the purpose of premedication. We compared pulse rate, blood pressure and respiratory rate as indirect measures for level of anxiety in the two groups.

Selection of patients: 40 patients were randomized into two groups of twenty each by computer generated randomization charts. The OTFC group contained 20 patients who received

200 microgram of Oral Trans mucosal Fentanyl and 20 patients of IMFC group received 100 microgram of Inj. Fentanyl intra-muscularly as premedication.

Inclusion Criteria:

- Adult patient 18–50 years.
- Both sexes
- Patients belonging to American Society of Aneasthesiologist physical status I & II.
- Patients who gave their consent for the study.
- Patients undergoing elective surgery under general anaesthesia.

Exclusion Criteria:

- Patient refusal for consent.
- Patients with known allergy to study drugs.
- Patients belonging to American Society of Anaesthesiologist physical status III and IV
- Patients with diabetes mellitus, hypertension or those who are put on drugs to control heart rate or blood pressure.
- Patients aged more than 50 years

Drugs used:

- Inj. Glycopyrrolate.
- Inj. Fentanyl
- Oral Trans mucosal Fentanyl Citrate.
- Inj. Rocuronium bromide.
- Inj. Neostigmine.

Monitors used:

- Pulse Oximeter
- NIBP
- ECG
- EtCO2
- Temperature monitoring.

METHODOLOGY: Patients were randomized by computer generated randomization charts, and divided into Group OTFC and Group IMFC. The premedication was given by the person not involved in the study after measuring the baseline vitals of the patients in the premedication area to blind the observer.

GROUP OTFC: 20 patients received 200 micrograms of Oral Trans mucosal Fentanyl Citrate (OTFC).

GROUP IMFC: 20 patients received 100 micrograms of Inj. Fentanyl Citrate.

After ascertaining the inclusion criteria preoperative investigations were recorded and assessed preoperatively. Patients were connected to multi Para monitor and ECG, Oxygen saturation (Pulse oximetry) and NIBP were monitored. Baseline vitals such as pulse rate, blood pressure, oxygen saturation and respiratory rate were recorded. Patients were pre medicated by Trans mucosal or Intramuscular Fentanyl. Patients were monitored in the pre-anaesthetic area for 30 minutes, and every 5 minute pulse rate blood pressure, respiratory rate and oxygen saturation were monitored. 30 minutes after premedication, the patients they were shifted to the operating theatre. Monitors were reconnected, pre anaesthetic check of Boyle's apparatus was done, Ambu bag, Airway gadgets, Emergency drugs were checked and kept available. All the patients underwent general anaesthesia with Inj. Glycopyrrolate 0.2 mg, Inj. Propofol 2mg/kg and Inj. Rocuronium 0.6 mg/ kg. Surgical procedure was started 15 minutes post intubation.

Patients pulse rate, respiratory rate, blood pressure and oxygen saturation were measured once the patient was put on operating table, during the induction of anaesthesia, post laryngoscopy, and three more readings at 5 minutes interval were recorded. Complications if any suffered by the patients in the peri-operative period were also noted.

Definition of terminologies defined for the study:

Pulse /SBP (Systolic Blood Pressure)/ DBP (Diastolic Blood Pressure) / RR (respiratory rate) at "0": measured variable in preoperative room before giving premedication. After the measurement premedication was given.

Pulse /SBP / DBP / Respiratory Rate (RR) at "5, 10, 15, 20, 25, 30": measured variable in preoperative room at 5/10/15/20/25/30 minutes after giving the premedication. 30 minutes after the premedication the patient was shifted to the operative room.

Pulse /SBP / DBP / Respiratory Rate (RR) at "A, B, C, D, E": measured variable in operative room after putting the patient on the operating table/ after induction of anaesthesia/ after intubation/ 5 minutes 10 minutes and 15 minutes thereafter.

Statistical analysis:

Variables were analyzed with SPSS version 20 software. Quantitative variables were analyzed using independent "t" test and qualitative variables were analyzed using cross tabs. 'p' value less than 0.05 was taken as significant.

Age, weight and gender distribution among the groups were comparable. Mean age and weight in the OTFC group were 37.75 years and 60.25 kg, and that in IMFC group were 38.7 years 59.65 kg. The variation in both was not statistically significant (table-1, figure 1).

GROUP	MEAN AGE IN YEARS	MEAN WEIGHT IN KILOGRAM
GROUP OTFC	37.75	60.25
GROUP IMFC	38.7	59.65
p value	0.745	0.376

Table 1: Mean age and weight of the patients in two groups

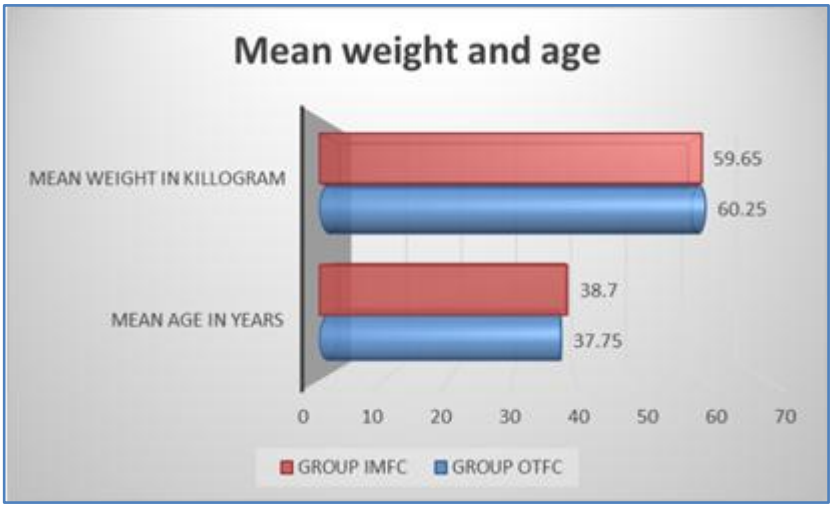

Fig. 1: Mean age and weight of the patients in two groups

17 patients in both the group belonged to American Society of Anaesthesiologist physical status I, and 3 patients in both groups belonged to ASA group II and hence they were comparable. Gender distribution among the two groups were comparable with OTFC group having 9 male patients and 11 female patients and IMFC group contained 11 male and 9 female patients. The variation showed the p value to be 0.527 and was statistically insignificant (table 2, figure 2).

GROUP	Number of male patients	Number of female patients
GROUP OTFC	9	11
GROUP IMFC	11	9
p value	0.527	

Table 2: Gender distribution in two groups

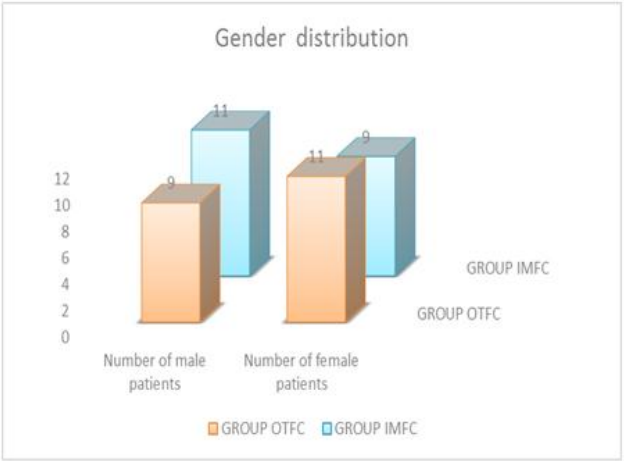

Fig. 2: Gender distribution in two groups

Pulse rate of the patients in the two groups were comparable at time '0', and the variation between group was found to be statistically significant at 5, 10, 15 minutes post administration of the premedication. The variation of pulse rate between the groups is shown in table 3 and figure 3.

GROUP	Pulse 0	Pulse 5	Pulse 10	Pulse 15	Pulse 20	Pulse 25	Pulse 30
GROUP OTFC	87.10	80.95	80.25	79.30	78.15	76.70	75.85
GROUP IMFC	87.40	94.10	88.40	86.05	81.20	78.50	76.50
p value	0.896	0.000	0.000	0.001	0.115	0.303	0.733

GROUP	Pulse A	Pulse B	Pulse C	Pulse D	Pulse E
GROUP OTFC	75.20	73.50	79.85	75.70	74.35
GROUP IMFC	76.50	74.75	80.90	76.25	75.35
p value	0.429	0.395	0.495	0.721	0.480

Table 3: Pulse rate variation in beats per minute between two groups

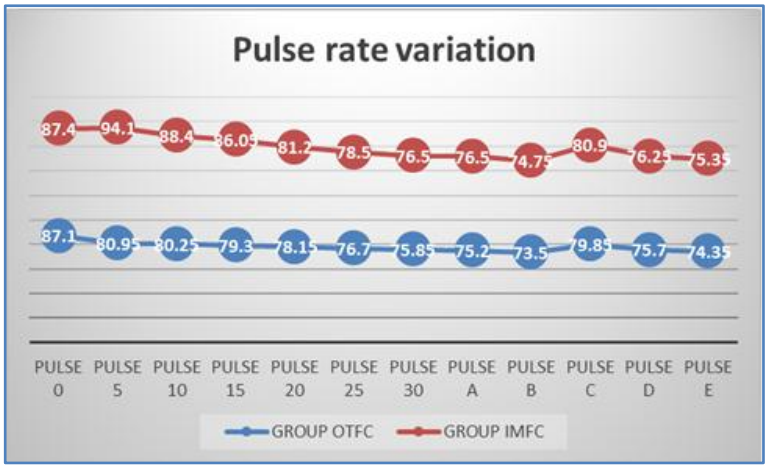

Fig. 3: Pulse rate variation in beats per minute between two groups

The Systolic Blood Pressure (SBP) variation between groups is as shown in table 4 and figure 4. The baseline SBP was comparable between the groups and the variation between the groups were significant at 5 and 10 minutes post premedication.

GROUP	SBP 0	SBP 5	SBP 10	SBP 15	SBP 20	SBP 25	SBP 30
GROUP OTFC	127.00	120.10	116.10	119.50	118.40	116.85	116.35
GROUP IMFC	125.10	129.80	125.10	121.85	119.25	117.65	116.40
p value	0.561	0.001	0.000	0.365	0.688	0.686	0.976

GROUP	SBP A	SBP B	SBP C	SBP D	SBP E
GROUP OTFC	117.60	103.90	124.85	118.20	116.50
GROUP IMFC	117.45	104.00	124.75	117.75	116.40
p value	0.936	0.957	0.963	0.864	0.964

Table 4: Systolic Blood Pressure variation in mm of Hg between two groups

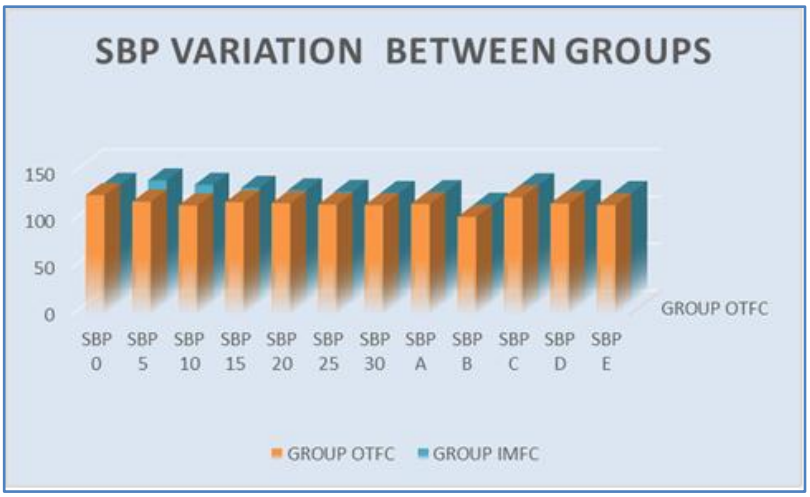

Fig. 4: Systolic Blood Pressure variation in mm of Hg between two groups

The Diastolic Blood Pressure (DBP) variation between groups is as shown in table 5 and figure 5. The baseline DBP were comparable between the groups and the variation between the groups were significant at 5, 10, 15, 20 minutes post premedication and 5 minutes post intubation (at C).

GROUP	DBP 0	DBP 5	DBP 10	DBP 15	DBP 20	DBP 25	DBP 30
GROUP OTFC	77.00	72.40	70.50	70.00	68.90	68.30	67.45
GROUP IMFC	77.30	87.55	80.05	75.80	72.35	70.35	69.05
p value	0.878	0.000	0.000	0.001	0.030	0.164	0.289

GROUP	DBP A	DBP B	DBP C	DBP D	DBP E
GROUP OTFC	66.20	55.80	75.90	68.90	64.35
GROUP IMFC	68.30	56.50	79.85	69.90	65.75
p value	0.132	0.583	0.001	0.364	0.261

Table 5: Diastolic Blood Pressure variation in mm of Hg between two groups

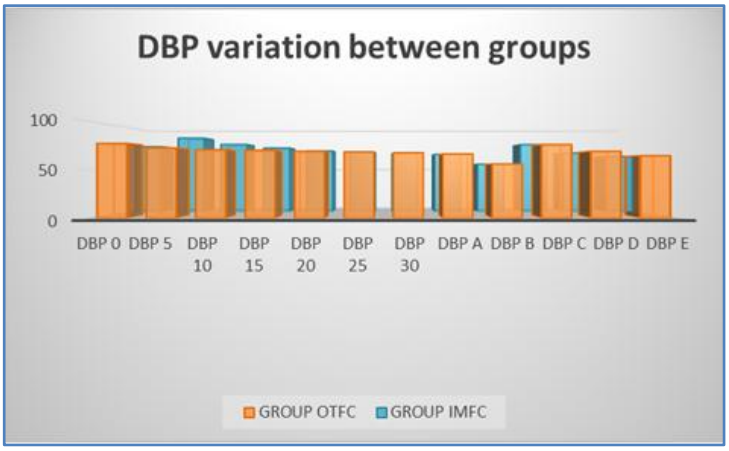

Fig. 5: Diastolic Blood Pressure variation in mm of Hg between two groups

Respiratory rate (RR) variation and oxygen saturation (SPO2) of patients during the study are tabulated as in table 6 and 7. The variation between groups did not show any statistical significance.

GROUP	RR 0	RR 5	RR 10	RR 15	RR 20	RR 25	RR 30	RR A
GROUP OTFC	13.05	13.25	13.10	13.15	12.95	13.00	13.20	12.85
GROUP IMFC	12.90	13.25	13.25	13.05	12.95	13.15	12.90	12.85
p value	0.560	1.00	0.645	0.730	1.00	0.657	0.342	1.00

Table 6: Respiratory Rate variation in cycles per minute between two groups

GROUP	SPO2 0	SPO2 5	SPO2 10	SPO2 15	SPO2 20	SPO2 25	SPO2 30
GROUP OTFC	95.80	95.20	95.75	96.10	96.20	96.50	96.20
GROUP IMFC	96.35	95.25	96.15	96.00	96.15	96.55	96.15
p value	0.57	0.857	0.137	0.746	0.895	0.886	0.859

GROUP	SPO2 A	SPO2 B	SPO2 C	SPO2 D	SPO2 E
GROUP OTFC	98.55	99.00	99.05	99.20	99.45
GROUP IMFC	98.50	99.00	99.00	99.15	99.20
p value	0.759	0.324	0.016	0.687	0.096

Table 7: Oxygen saturation variation between two groups

No patients in the study period had events of hypoxia following premedication. Adverse effects such as nausea and vomiting, pruritus and drowsiness are shown in table 8.

None of the patients in the OTFC group had nausea, 3 patients had vomiting and 5 patients had drowsiness in this group. 4 patients in the IMFC group had nausea and vomiting, 6 patients had pruritus and 4 patients had drowsiness in this group. The statistical analysis showed adversities such as nausea and pruritus to be significantly high in IMFC group.

GROUP	Nausea	Vomiting	Pruritus	Drowsiness
GROUP OTFC	0	3	0	5
GROUP IMFC	4	4	6	4
p value	0.035	0.677	0.008	0.705

Table 8: number of patients suffering from various adverse effects

RESULTS: In our randomized prospective clinical study, 40 patients were divided into two groups of 20 each. In the group OTFC, patients received 200 microgram of OTFC and in the IMFC group the patients received 100 microgram of Inj. Fentanyl Citrate intramuscularly. The study was aimed to find the efficacy of Trans mucosal route of drug administration against intramuscular route.

The two groups were comparable in the basal demographic parameters such as age, gender distribution and weight of the patients. Patients also showed comparability in terms of ASA physical status. The baseline pulse rates were comparable in the two groups, but the pulse rate variability became statistically significant at 5, 10 and 15 minutes post premedication. The pulse rate in OTFC group at 5, 10, 15 minutes were 80.95, 80.25 and 79.30 beats per minute corresponding values in IMFC group were 94.10, 88.40 and 86.05 beats per minute. The pulse rate at 5, 10 and 15 minutes were higher and the p value at the same time was 0.000, 0.000 and 0.001. Similarly the baseline SBP was comparable in both groups and the variation in the SBP became statistically significant at 5 and 10 minutes post premedication, in OTFC group.

SBP at 5 and 10 minutes were 120.10 and 116.10 mm of Hg and that in IMFC group were 129.80 and 125.10 mm of Hg and it was higher in group IMFC on both occasions. The p value for the variation were 0.001 and 0.000 respectively. The DBP also showed statistically significant variation at 5, 10, 15, 20 minutes post premedication and 5 minutes post intubation (C). The DBP at 5, 10, 15, 20 and C were 72.40, 70.50, 70.00, 68.90 and 75.90 mm of Hg in OTFC group, the DBP in IMFC group at 5, 10, 15, 20 and C were 87.55, 80.05, 75.80, 72.35 and 79.85 mm of Hg respectively.

Not only DBP at these occasions were found to be higher in IMFC group but also the variations were statistically significant with p value 0.000, 0.001, 0.030. There were no statistically significant variation in the rate of respiration and oxygen saturation in both the groups in the study duration. Adverse effects like nausea, vomiting, pruritus drowsiness and desaturation were monitored. 4 patients in IMFC group had nausea and 6 patients in IMFC group had pruritus as compared to none of the patients in OTFC group had nausea and pruritus, this was found to be statistically significant with p value of 0.035 and 0.008.

DISCUSSION: Use of Trans mucosal Fentanyl averted the transient needle phobia and the associated physiological response to needle prick. Anxiety causes increased postoperative pain, delayed recovery from anaesthesia, larger dose of anaesthetic drug requirement and also prolongs the hospital stay.[7- 9] Also the baseline vitals on the day of surgery which is altered by the anxiety can lead on to alteration in the procedures, dictate the dosage of drugs and can also lead to abandonment of the procedures at times.

Hence anxiolytics have been given place in the premedication, but the mode of administration of these premedication mostly involves a needle prick and this can trigger the anxiety for a short period. Alternate ways of drug administration for the same has been in pursuit. Trans mucosal route of drug administration is noninvasive, convenient and more easily acceptable for the patients. Buccal mucosa being highly vascular and has a large surface area which is drained into superior venacava, highly lipid soluble drugs are absorbed rapidly and bypass the first pass metabolism in the liver. Trans mucosal rate promises four times more rapid drug delivery compared to transdermal route of drug delivery.[10]

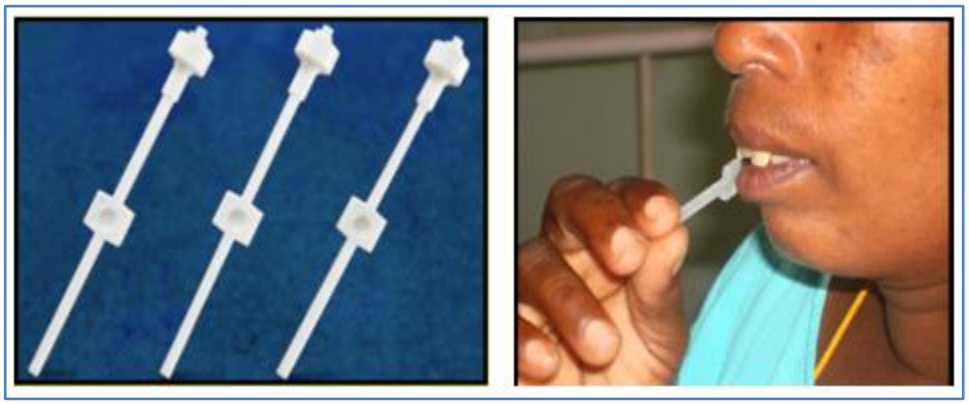

Fig. 6: Transmucosal Fentanyl and the Patient Using Transmucosal Fentanyl

OTFC has been used with good effect in the patients having break through cancer pain. OTFC is manufactured in matrix of sucrose, liquid glucose and the lozenge is fitted on to radiopaque handle. Available in 200, 400, 600, 800, 1200 and 1600 microgram. It is very similar to intramuscular (i.m) or intravenous (i.v) Fentanyl in pharmacodynamics point of view. As against i.m or i.v route, in trans mucosal route plasma concentration of drug is halved. Peak concentration of drug occurs in 20 minutes, and action lasts for as long as 2.5-5 hours.[11] 25% of the administered Fentanyl is rapidly absorbed from the buccal mucosa and again 25% of the drug gets absorbed slowly from the Gastro-intestinal system and 50% of the drug gets wasted in metabolism or excreted.

CONCLUSION: Trans mucosal route of Fentanyl administration is as effective as the intramuscular route of Fentanyl administration for premedication and is devoid of physiologic response to needle prick.

Drawbacks of the study:

- Patient blinding was not possible.
- Number of patients involved in the study was small and this study can be considered as pilot study.

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