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A Comparative Evaluation of Intravenous Dexmedetomidine Versus Intravenous Fentanyl For Attenuation Of Pressor Response To Laryngoscopy And Endotracheal Intubation.

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Abstract:
Background*: Airway control during general anaesthesia is provided by laryngoscopy and endotracheal intubationLaryngoscopy and endotracheal intubation lead to mechanical and chemical stimuli. Mechanical stimulus causes reflex responses in cardiovascular and respiratory systems. That response reaches its maximum level within 1 min and ends in 5-10 min after endotracheal intubationOn the other hand, chemical stimulus results with catecholamine release via increase in sympatho-adrenergic activity. Catecholamine release leads to hypertension, tachycardia and arrhythmia. Tachycardia generates a more powerful load on the heart when compared with hypertension as it increases oxygen consumption of the myocardium, decreases diastolic filling and finally reduces coronary blood supply. Which can be deleterious to the patient the aim of our study was to compare effects of iv fentanyl with dexmedetomidine in attenuating the pressor response during laryngoscopy and intubation*
Materials and Methods*: In this prospective randomisedcohort observational study, 80 patients of ASA physical status I and II belonging to age group of 18-65 years scheduled for elective non cardiac surgery under general anaesthesia the patients were randomly devided into two groups (n=40).Group D receive 1 mcg/kgof dexmedetomidine bolus iv over 15 min prior to induction and Group F will receive fentanyl in a dose of 2 mcg/kg prior to induction. All the patients were uniformly premedicated, induced with propofol and atracurium as per standard protocol heart rate and blood pressure recorded at baseline after study drug infusion, after induction , immediately and 1,3,5,10 min after intubation*
Results*:Demographic parameters were comparable between the groups. The heart rate was significantly less after infusion, over 15 min ,induction, immediate and 1 ,3, minute after intubation, systolic blood pressure was less after infusion over 15 min and 10 min after intubation,in dexmedetomidine group as compare with fentanyl and diastolic blood pressure and mean arterial pressure is equivalent between both dexmedetomidine and fentanyl.*
Conclusion:*Both fentanyl and dexmedetomidine attenuated the pressor response.Of the two drugs administered dexmedetomidine 1µg / kg provides a reliable, consistent and effective attenuation of pressor response as compared to fentanyl mcg/kg*
Key Word*:* Dexmedetomidine, Fentanyl, Intubation, laryngoscopy, hemodynamic response

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I. Introduction

During general anaesthesia airway control is generally provided by laryngoscopy and endotracheal intubation. Laryngoscopy and endotracheal intubation lead to mechanical and chemical stimuli. Mechanical stimulus causes reflex responses in cardiovascular and respiratory systems. That response reaches its maximum level within 1 min and ends in 5-10 min after endotracheal intubation. On the other hand, chemical stimulus results with catecholamine release via increase in sympatho-adrenergic activity. Catecholamine release leads to hypertension, tachycardia and arrhythmia. Tachycardia generates a more powerful load on the heart when compared with hypertension as it increases oxygen consumption of the myocardium, decreases diastolic filling and finally reduces coronary blood supply.[1,2,3] The degree of the reflex response of laryngoscopy and intubation is related with the depth of anesthesia, patient's age and the presence of diabetes or heart disease. Narcotic analgesics, Magnesium sulphate, local anesthetics, beta-blockers, calcium channel blockers, alpha 2 adrenergic agonist and vasodilators are employed in order to control that response. . Fentanyl citrate is a narcotic

analgesic interacting predominantly with the opioid μ receptor and exerting its principal pharmacological effect on CNS. Its primary action of therapeutic value is analgesia and sedation. It is extensively used for anaesthetic and analgesic most often in operating room and ICU [4] Dexmedetomidine is a selective alpha 2 adrenergic agonist. Its effects on cardiovascular system are particularly prominent. Dexmedetomidine is an imidazole derivative produce hyperpolarization of noradrenergic neurons and suppression of neuronal firing in the locus cerelous leads to decreased systemic noradrenaline release results in attenuation of sympatho-adrenal responses and hemodynamic stability during laryngoscopy and tracheal intubation. The topic of study was selected because numerous drugs have been tried in varying doses to attenuate the laryngoscopy response to intubation, but with limited success rate only. [5] The reason being the underlying side-effect profile that the drug carries at varying doses. Hence, there is a constant research for a drug that attenuates laryngoscopy response, has 10 fewer side-effects that could be counteracted with minimal interventions, easy availability, cost effectiveness and can be used in maximum number of patients posted for surgery under general anaesthesia belonging to various ASA grades. In this single center, prospective randomized cohort observational study we conducted, we wished to compare the extent of attenuation of pressor response to Laryngoscopy and Endotracheal Intubation by two commonly used drugs namely Fentanyl and Dexmeditomedine. The effect of the two drugs on the hemodynamic parameters such as heart rate systolic blood pressure, diastolic blood pressure, mean blood pressure and spo2 changes in patients undergoing various surgeries at the time of when patient shifted to operation theatre, at the end of infusion of drug, induction of Anesthesia, immediately after intubation and subsequently at 1, 3, 5 and 10 minutes after intubation. In this context, the study we proposed compared the safety and efficacy of infusion IV dose of dexmedetomidine with single bolus IV dose of fentanyl in attenuating hemodynamic response to laryngoscopy and tracheal intubation

II. Material And Methods

This prospectiverandomized cohort observational studywas carried out on patients of Department of anaesthesia atKokilabendhirubhai Ambani Hospital and Medical Research Institute, Andheri (West), Mumbai 400053 ,Maharashtra from April 2021 to September 2021. A total 90 adult subjects (both male and females) of aged 18-65 years were for in this study.

Study Design: Prospective randomized cohort observational study

Study Location: Department of anaesthesia at Kokilabendhirubhai Ambani Hospital and Medical Research Institute, Andheri (West), Mumbai 400053 ,Maharashtra

Study Duration: April 2021 to September 2021

Sample size: 90 patients.

Sample size calculation: The Sample size was calculated using the HR values at 10 minutes after intubation for Dexmedetomidine and Fentanyl as reported in a study by Mahjoubifard et al 2020. Sample size was calculated to achieve 80% power of the study at 95% confidence interval. Sample size was calculated to be 36 for each group. Considering a drop out rate of 10%, 40 patients would be recruited in each group. i.e. a total of 80 patients will be included in the study. Where: 23 n = sample size 燎1 = standard deviation of Group 1 燎2 = standard deviation of Group 2 潴= difference in group means 昜= ratio = n2/n1 Z1-α/2 = two-sided Z value (eg. Z=1.96 for 95% confidence interval). Z1-β = power

Subjects & selection method: 80 patients of ASA I and ASAII grade between 18-65yr scheduled for elective surgery under general anaesthesia pertaining to various operative departments including, but not restricted to general surgery, gynecology, ENT, orthopedics requiring endotracheal intubation. Informed written consent for study in patient's language was taken and they were divided into 2 groups of 40 patients each by computer generated PFA randomization.

With Group D (n=40): Dexmedetomidine group will receive dexmedetomidine infusion before induction of anaesthesia Group F (n=40): Fentanyl group will receive IV fentanyl before induction of anaesthesia.

Inclusion criteria:1) Patients who would voluntarily agree to sign informed consent form
2) American society of Anaesthesiologists (ASA) physical status I/II patients
3) Patients aged between 18-65 yr
4) Patients with both male and female gender
5) Patients scheduled for elective surgery under general anaesthesia.

Exclusion criteria:

1. Patients with anticipated difficult airway.
2. Patient with sever LV dysfuction(EF<35)
3. Allergy or contraindication to drugs used in study
4. Morbid obesity (BMI>40%)
5. Intubation longer than 15 sec

6. Patient with Hypotension(SBP
7. Females who are pregnant, lactating.
8. Patient with hepatic or renal disease
9. Chronic obstructive pulmonary
10. Patient with bradyarrythmia or tachyarrythmias.

Procedure methodology

After written After clearance from the scientific and ethical committee of the institute for thesis synopsis is received, study was initiated on patients meeting the study requirements. On the day prior to surgery a thorough pre-operative assessment of the patient was performed including General Physical Examination & systemic examination. All patients were explained about the anaestheia technique & written informed consent was taken. Patients were kept NPO for 6 hrs prior to surgery. Patient were allocated into one of the study groups (Group D or Group F) by computer based PFA randomization In the operating room, standard monitors (electrocardiogram, Noninvasive blood pressure and pulse oximeter) were attached to the patient, and baseline vitals namely heart rate (HR),pulse oximetry (SPO2), Electrocardiogeram (ECG) were recorded. The observations were made by an anaesthesiologist who was aware of the study drug. Anaesthesia technique: Anaesthesia machine, breathing circuits will be checked and resuscitation equipments were kept ready. Continous monitoring of the vital parameters was done. Pre-medication with intravenous gylcopyrolate 0.2mg and midazolam 1mg was given to all study patients . Group D patients received intravenous dexmedetomidine 1µg per kg in 50ml normal saline infused over 15 mins. Group F patients received intravenous fentanyl in a dose of 2mcg/kg (10mg/cc) beforeinduction of anaesthesia. 25 Induction of ananesthesia was carried out with intravenous (i.v) propofol in a dose of 2mg/kg followed by i.v atracurium 0.5mg/kg to provide neuromuscular blockade. The patient was ventilated through bag and mask with 100% oxygen with close circuit for next 3 minutes. Thereafter, laryngoscopy and intubation was performed by an experienced anaesthesiologist with Macintosh laryngoscope 3 or 4 and intubation performed with a cuffed endotracheal tube of appropriate size with strict and vigilant monitoring of hemodynamic and respiratory parameters at regular intervals of 1 minute, 3 minute, 5 minute and 10 minute after intubation. Surgery commenced at the end of 10min after laryngoscopy & intubation. No form of stimulus was applied during the study period. A 20% increase in HR and MAP above baseline was regarded as positive response to intubation Vital parameters were recorded at following points of time: 1. Baseline reading when the patient is shifted to the OT (T0) 2. After infusion over 15 minutes. (Ti) 3. After induction of anaesthesia. (Ta) 4. Immediately after intubation. (Te) 5. At 1 minute after intubation. (T1) 6. At 3 minute after intubation.(T3) 7. At 5 minute after intubation.(T5) 8. At 10 minute after intubation.(T10)

Statistical analysis

Data was analysed using SPSS/ Excel. ꝏ Normality of continuous data would be accessed using Shapiro Wilk test. ꝏDifference in normally distributed data of 2 groups would be analysed using Independent Sample T test and non-normally distributed sample would be analysed using Mann Whitney U test. ꝏChange in parameters at different time intervals will be assessed using Paired sample T test (for normally distributed data) and by Wilcoxon Signed Rank test (for not normally distributed data). ꝏCross tabulations will be commuted according to anaesthesia group and compared using chi-square/ Fisher Exact Test. $P< 0.05$ will be considered to be statistically significant

III. Result

Table number 1. Characteristics of the patients (Age , gender, BMI, ASA and MPC)

	Group 1 (Fentanyl)	Group 2 (Dexmedetomidine)	P value
Age (in years)	44.95 +/- 11.31	45.82 +/- 11.11	0.72
Gender (Male %)	17 /40 (42.5%)	12/40 (30%)	0.35
BMI (kg/m^2)	24.30 +/- 4.23	25.66+/- 3.49	0.12
Proportion of patients with ASA I (%)	27/40 (67.5%)	25/40 (62.5%)	0.81
Proportion of patients with MPC I (%)	19/40 (47.5%)	25/50 (62.5%)	0.26

The baseline characteristics of the patients are presented in table above.

The average age in the Fentanyl group was 44.9 years and that in the Dexmedetomidine group was 45.82 years. Upon comparing, the difference is not statistically significant. (p v value 0.72). It means that the two groups are comparable with respect to age.

The proportion of males in the Fentanyl group was 42.5% and that in the Dexmedextomidine group was 30%. Upon comparing, the difference is not statistically significant. (p value 0.35).
The average BMI in the Fentanyl group was 24.3 kg/m^2 while that in the Dexmedetomidine group was 25.6 kg/m^2. Upon comparing, the difference is not statistically significant (p value 0.12). It means that the two groups are comparable with respect to BMI.
There were no patients with ASA III or above in either group. The proportion of patients with ASA I was 67.5% in the Fentanyl group. The proportion of patients with ASA I in the Dexmedetomidine group was 62.5%. Upon comparing, the difference is not statistically significant (p value 0.81). It means that the two groups are comparable with respect to the ASA grades.
There were no patients with MPC III or above in either group. The proportion of patients with MPC I was 47.5% in the Fentanyl group. The proportion of patients with MPC I in the Dexmedetomidine group was 62.5%. Upon comparing, the difference is not statistically significant (p value 0.26). It means that the two groups were comparable with respect to MPC status.
In summary, both the groups were comparable in their baseline characteristics.

Figure number 1. Comparison of heart rate changes between groups at specified time intervals

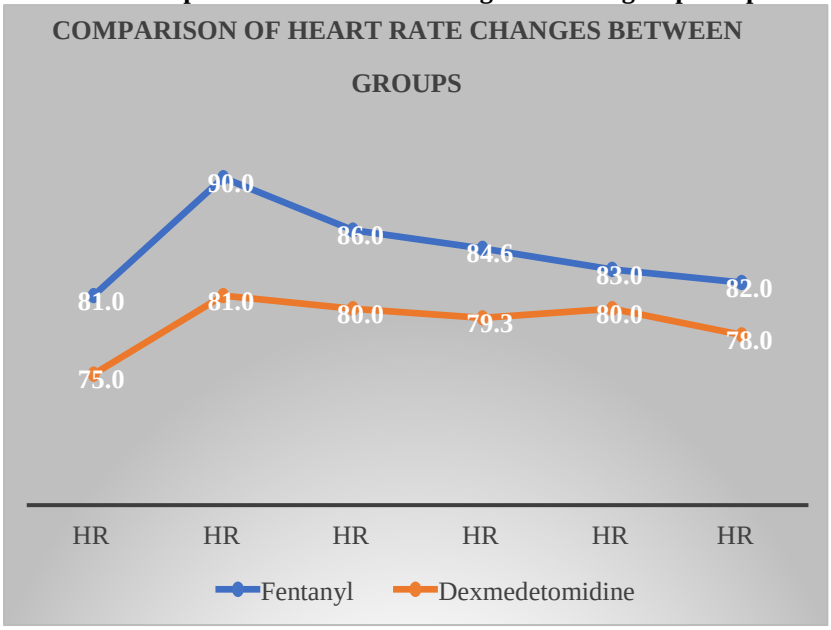


Table number 2. Heart rate changes at the specified time intervals

Heart rate	Group 1 (Fentanyl)	Group 2 (Dexmedetomidine)	P value
Baseline reading when the patient is shifted to the OT (T0)	80.72 +/- 10.78	79.67+/- 7.94	0.62
After infusion over 15 minutes. (Ti)	79.32 +/- 10.27	66.82 +/- 6.97	**<0.0001***
After induction of anaesthesia. (Ta)	81.87 +/- 8.69	75.37 +/- 7.86	**0.0007***
Immediately after intubation. (Te)	90.95 +/- 7.47	81.57 +/- 10.66	**<0.0001***
At 1 minute after intubation. (T1)	86.62 +/- 8.04	80.4+/- 8.87	**0.001***
At 3 minute after intubation.(T3)	84.6 +/- 8.66	79.35 +/- 8.98	**0.009***
At 5 minute after intubation.(T5)	83.52 +/- 9.38	80.1+/- 8.73	0.09
At 10 minute after intubation.(T10)	82.65 +/- 9.81	78.82 +/- 10.59	0.09

*Statistically significant

The baseline heart rate in the Fentanyl group was 80 beats per minute and in the Dexmedetomidine group was 70 beats per minute and there was no statistically significant difference between the groups. This means that the baseline heart rate between the groups were comparable.

The Ti (after infusion over 15 minutes) showed a much higher reduction in heart rate with dexmedetomidine compared to fentanyl (p value <0.0001).

The Ta (after induction of anesthesia) showed a much higher reduction in heart rate with dexmedetomidine compared to fentanyl (p value 0.0007)

The Te (immediately after intubation) showed a much higher reduction in the heart rate with dexmedetomidine compared to fentanyl (p value <0.0001)

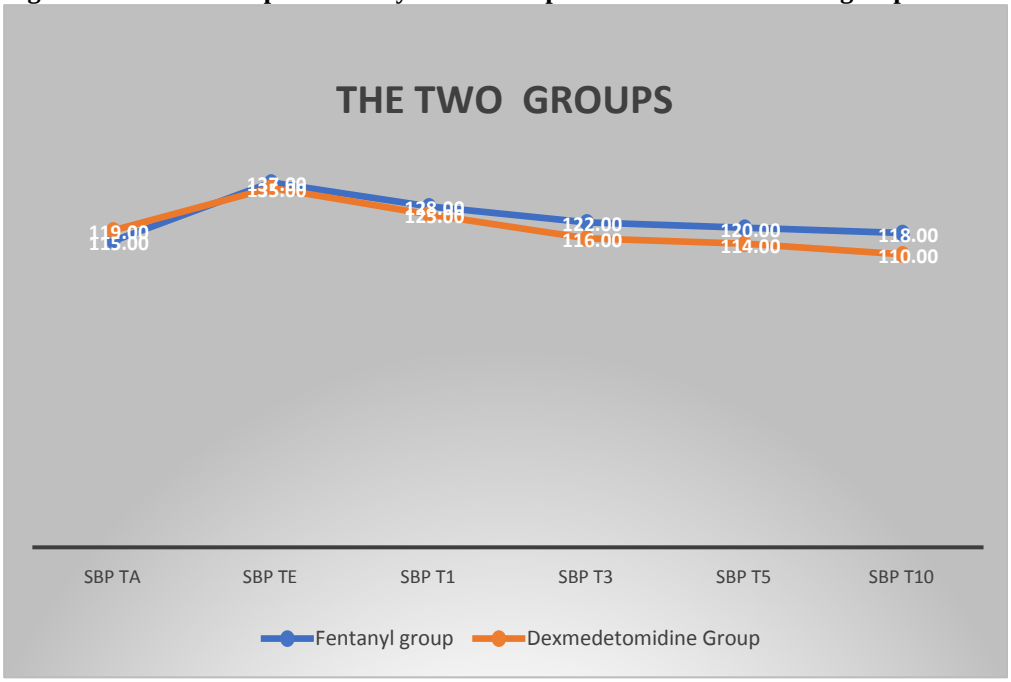
The T1 (1 minute after intubation) showed a much higher reduction in the heart rate with dexmedetomidine compared to fentanyl (p value 0. 001)

The T3 (3 minute after intubation) showed a much higher reduction in the heart rate with dexmedetomidine compared to fentanyl (p value 0. 009)

The T5(5 minute after intubation) did not show any difference in the heart rate between the groups (p value 0. 09)

The T10 (5 minute after intubation) did not show any difference in the heart rate between the groups (p value 0. 09)

Figure number 2. Comparison of systolic blood pressure between the two groups



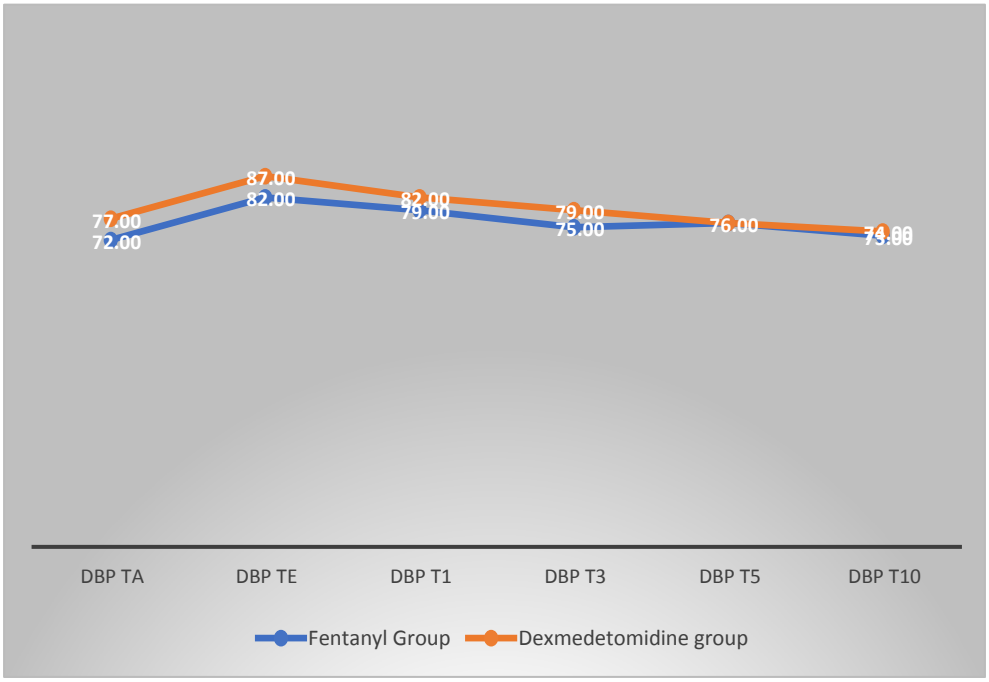
COMPARISON OF SYSTOLIC BLOOD PRESSURE BETWEEN

Table number 3. Systolic Blood Pressure changes at the specified time intervals

Systolic Blood pressure	Group 1 (Fentanyl)	Group 2 (Dexmedetomidine)	P value
Baseline reading when the patient is shifted to the OT (T0)	136.1+/- 16.18	133.7+/- 14.03	0.48
After infusion over 15 minutes. (Ti)	133.25 +/- 15.72	125.52 +/- 15.76	**0.031***
After induction of anaesthesia. (Ta)	115.62 +/- 15.74	119.87 +/- 16.40	0.24
Immediately after intubation. (Te)	137.4 +/- 16.18	135.82 +/- 18.42	0.68

At 1 minute after intubation. (T1)	128.65 +/- 18.77	125.25 +/- 21.05	0.44
At 3 minute after intubation.(T3)	122.7 +/- 18.93	116.52 +/- 16.95	0.12
At 5 minute after intubation.(T5)	120.42 +/- 17.29	114.07 +/- 17.33	0.10
At 10 minute after intubation.(T10)	118.4 +/- 17.08	110.75 +/- 15.34	**0.038***
***Statistically significant**			

The baseline systolic blood pressure in the Fentanyl group was 136 mmHg and in the Dexmedetomidine group was 133 mmHg and there was no statistically significant difference between the groups. This means that the baseline systolic blood pressure between the groups were comparable.
The Ti (after infusion over 15 minutes) showed a much higher reduction in the systolic blood pressure with dexmedetomidine compared to fentanyl (p value 0.031).
The Ta (after induction of anesthesia) did not show any difference in the systolic blood pressure between the groups (p value 0.24)
The Te (immediately after intubation) did not show any difference in the systolic blood pressure between the groups (p value 0.68)
The T1 (1 minute after intubation) did not show any difference in the systolic blood pressure between the groups (p value 0.44)
The T3 (3 minute after intubation) did not show any difference in the systolic blood pressure between the groups (p value 0.12)
The T5 (5 minute after intubation) did not show any difference in the systolic blood pressure between the groups (p value 0.10)
The T10 (10 minute after intubation) showed a much higher reduction in the systolic blood pressure with dexmedetomidine compared to fentanyl (0.038).
In summary, dexmedetomidine showed a better reduction in the systolic blood pressure when compared to fentanyl at 10 minutes following intubation and after infusion over 15 minutes; but not at the other time periods.
Figure number 3. Comparison of Diastolic blood pressure between groups



Comparison of Diastolic Blood pressure between groups

Table number 4.Diastolic Blood Pressure changes at the specified time intervals

Diastolic Blood pressure	Group 1 (Fentanyl)	Group 2 (Dexmedetomidine)	P value
Baseline reading when the patient is shifted to the OT (T0)	82.37 +/- 11.9	82.52 +/- 8.58	0.94
After infusion over 15 minutes. (Ti)	79.9 +/- 10.07	79.12 +/- 10.66	0.73
After induction of anaesthesia. (Ta)	72.72 +/- 10.1	77.4 +/- 13.6	0.077
Immediately after intubation. (Te)	82.8 +/- 11.71	87.77 +/- 12.42	0.069
	79.37 +/-	82.15 +/-	0.302
At 1 minute after intubation. (T1)	9.31	14.09	
At 3 minute after intubation.(T3)	75.4 +/- 10.6	79.12 +/- 13.2	0.169
At 5 minute after intubation.(T5)	75.6 +/- 9.93	76.27 +/- 12.04	0.79
At 10 minute after intubation.(T10)	73.42 +/- 8.84	74.35 +/- 11.54	0.68

The baseline diastolic blood pressure in the Fentanyl group was 82 mmHg and in the Dexmedetomidine group was 82 mmHg and there was no statistically significant difference between the groups. This means that the baseline diastolic blood pressure between the groups were comparable.

The Ti (after infusion over 15 minutes) did not show any difference in the diastolic blood pressure between the groups (p value 0.73).

The Ta (after induction of anesthesia) did not show any difference in the diastolic blood pressure between the groups (p value 0.077)

The Te (immediately after intubation) did not show any difference in the diastolic blood pressure between the groups (p value 0.069)

The T1 (1 minute after intubation) did not show any difference in the diastolic blood pressure between the groups (p value 0.302)

The T3 (3 minute after intubation) did not show any difference in the diastolic blood pressure between the groups (p value 0.169)

The T5 (5 minute after intubation) did not show any difference in the diastolic blood pressure between the groups (p value 0.79)

The T10 (10 minute after intubation) did not show any difference in the diastolic blood pressure between the groups (0.68).

In summary, dexmedetomidine and fentanyl showed a similar profile of diastolic blood pressure reduction at all time intervals.

Figure number 4. Comparison of mean arterial pressure changes between the groups.

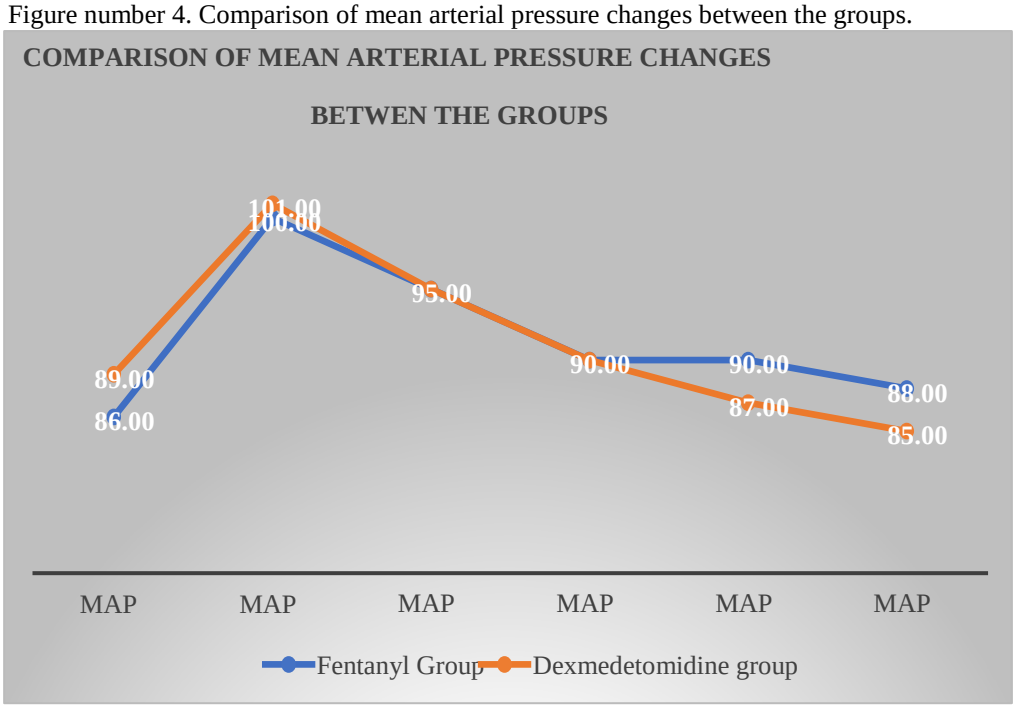


Table number 5. **Mean arterial Pressure changes at the specified time intervals**

Mean arterial pressure	Group 1	Group 2	P value
Baseline reading when the patient is shifted to the OT (T0)	99.57 +/- 11.52	97.55 +/- 10.52	0.40
After infusion over 15 minutes. (Ti)	97.52 +/- 10.42	93.17 +/- 11.85	0.085
After induction of anaesthesia. (Ta)	86.52 +/- 10.76	89.77 +/- 12.98	0.22
Immediately after intubation. (Te)	100.3 +/- 11.65	101.12 +/- 13.64	0.77
At 1 minute after intubation. (T1)	95.37 +/- 11.41	95.32 +/- 15.66	0.98
At 3 minute after intubation.(T3)	90.92 +/- 13.00	90.8 +/- 14.15	0.96
At 5 minute after intubation.(T5)	90.25 +/- 11.67	87.82 +/- 12.80	0.37
At 10 minute after intubation.(T10)	88.12 +/- 11	85.65 +/- 12.23	0.34

The baseline mean arterial pressure in the Fentanyl group was 99.57 mmHg and in the Dexmedetomidine group was 97.55 mmHg and there was no statistically significant difference between the groups. This means that the mean arterial pressure between the groups were comparable.

The Ti (after infusion over 15 minutes) did not show any difference in the mean arterial pressure between the groups (p value 0.085).

The Ta (after induction of anesthesia) did not show any difference in the mean arterial pressure between the groups (p value 0.22)
The Te (immediately after intubation) did not show any difference in the mean arterial pressure between the groups (p value 0.77)
The T1 (1 minute after intubation) did not show any difference in the mean arterial pressure between the groups (p value 0.98)
The T3 (3 minute after intubation) did not show any difference in the mean arterial pressure between the groups (p value 0.96)
The T5 (5 minute after intubation) did not show any difference in the mean arterial pressure between the groups (p value 0.37)
The T10 (10 minute after intubation) did not show any difference in mean arterial pressure between the groups (0.34).
In summary, dexmedetomidine and fentanyl showed a similar profile of mean arterial pressure reduction at all time intervals.

IV. Conclusion

Among patients undergoing general anesthesia and intubation prior to surgery, the usage of dexmedetomidine appears to have a better profile than fentanyl in terms of reduction of heart rate in response to tracheal intubation.
The control of systolic blood pressure is better with dexmedetomidine than fentanyl after 15 minutes of iv infusion, and after 10 minutes of intubation, but not at other time intervals.
The control of diastolic blood pressure is equivalent between both dexmedetomidine and fentanyl.
The mean arterial pressure is equivalent between both dexmedetomidine and fentanyl groups.

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