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Fentanyl and Dexmedetomidine: A Comparative Study of Effects on Hemodynamic Response to Laryngoscopy, Intubation and Peri-Operative Analgesia

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Abstract
The neurovegetative response to laryngoscopy and intubation has been a critical perioperative concern. Numerous pharmacological agents, such as opioids, local anaesthetics, β-blockers and α2 agonists has been tried to attenuate the haemodynamic challenge and augment analgesia. Dexmedetomidine is an α2 adrenoceptor, while fentanyl is a μ receptor opioid agonist, both drugs have been clinically tried in various clinical role in anaesthesia practice. They have been claimed to produce sedation, anxiolysis, hypnosis, analgesia, and sympatholysis individually. Dexmedetomidine has been further found to have opioid sparing effect while fentanyl has been used in clinical practice as a sole anaesthetic that blunts the sympathetic response during intubation. These variable characteristics of two drugsare the point of consideration in the present study to compare their effects on haemodynamic response to laryngoscopy and analgesia.
Keywords: *Dexmedetomidine, Fentanyl, Hemodynamic response, Laryngoscopy, Intubation.*

Introduction

The hemodynamic responses to laryngoscopy and endotracheal intubation is an outcome of laryngosympathetic reflexes due to epipharyngeal and laryngopharyngeal instrumentation[1]. Since its first description by Reid and Brace in 1940, this neurovegetative response has always been a challenge for the anaesthesiologists to attenuate this response and minimize the tachycardia, arrhythmias and acute rise in blood pressure[2,3]

The tremendous stress of laryngoscopy and endotracheal intubation results in increased level of catecholamines, an increase in plasma nor-epinephrine levels and to lesser extent epinephrine.[4,5]

This short lasting stress response is associated with increased morbidity and mortality particularly in patients with recent myocardial infarction, hypertension, pre-eclampsia, thyrotoxicosis and cerebrovascular pathology[6].

The prevention of detrimental effects of laryngoscopy and intubation on cardiovascular

system is of utmost importance and there is a need of safe and effective drug to attenuate the haemodynamic responsiveness. Several pharmacological agents have been used alone or in combination to achieve this effect. But, no pharmaceutical agent to date has been absolutely free of complications in part due to the unique chemical characteristics of each drug and their interaction with the individual biological system of each patient[7].

Opioids were the commonest agents used and appeared to obtund the response in a dose-related manner. Fentanyl, like morphine, meperidine, oxycodone, and others, a synthetic μ opioid receptor agonist produces the usual μ opioid central nervous system actions such as fatigue, sedation, nausea, vomiting, dizziness, respiratory depression leading to apnoea in higher doses and anaesthesia in higher doses irrespective of the mode of administration[8]. Fentanylintravenous low dose supplemental bolus has been claimed to cause modest changes in heart rate and blood pressure an effect secondary to central vagal stimulation.[9] Dexmedetomidine is a highly selective α_2-adrenoreceptor agonist that induces sedation and analgesia without affecting respiratory status. Dexmedetomidine reduces arterial blood pressure, heart and the hemod-ynamic responsiveness and plasma catecholamine response to intubation and extubation in ophthalmic and vascular surgeries.[10,11]

The variable characteristics of the two drugs with a common aim of attenuation of haemodynamic responsiveness and facilitate the perioperative analgesia, has been the purpose of this study through a prospective randomized double blind trial. The haemodynamic responsiveness was evaluated by measuring the change in blood pressure (SBP, DBP, MAP) and heart rate following laryngoscopy, endotracheal intubation and extubation. The perioperative analgesia was measured by the time of rescue analgesic administration. Further the incidence of side effects such as headache, nausea, vomiting were also recorded.

Material & Method

After due permission from Hospital Ethics Committee and written informed consent, patients undergoing laryngoscopy or endotracheal intubation under general anaesthesia for diagnostic/therapeutic purposes in were enrolled in this study. The sample size was calculated[12]

$$N = \frac{(r+1)(Z_{\alpha/2} + Z_{1-\beta})^2\sigma^2}{rd^2}$$

Where Z_α is the normal deviate at a level of significance (Z_α is 1.96 for 5% level of significance) and $Z_{1-\beta}$ is the normal deviate of type II error (0.84 at 80% power), r = n1/n2 is the ratio of sample size required for 2 groups, generally it is 1. σ and d are the pooled standard deviation and difference of means of 2 groups respectively, Where d=6.5 mmHg (post-intubation MAP difference), σ=15.5 mm Hg(pooled standard deviation), the sample size is 46.324≅ 46. The final adjusted sample size was kept 60 to obviate observational bias and 10% non-response rate.

A prospective, randomized, double blind, comparative study carried out in patients aged 18-60 years of ASA Grade I / II,using a sealed-envelope method. The patients were randomly divided into two equal groups.Group I, (n- 30) were infused a dexmedetomidine, a loading dose of 1 μg/kg intravenous and a maintenance dose of 0.4 μg/kg/hr; by continuous intravenous infusion. Group II, (n- 30) were infused fentanyl, a loading dose 1μg/kg intravenous bolus and a maintenance dose of 1μg/kg/hr continuous intravenous infusion. The loading doses were administered just prior to induction, infusion of maintenance dose were started and infusions were discontinued 30 min prior to end of surgery. The bolus dose was made in a total of 10 ml for the either group and continuous infusion dose was made in 50 ml to deliver the calculated maintenance dose at a fixed rate of infusion.

Patients were fasted for six hours before study. All patients were premedicated with Midazolam 0.05 mg/kg, Glycopyrrolate 0.004 mg/kg and Fentanyl 50 μg intravenous 30-60 minutes prior to surgery.

After preoxygenation with 100% oxygen anaesthesia, Group I & Group II patients were given their bolus doses respectively and induced with Propofol 2 mg/kg. The intubation and maintenance of muscle relaxation was achieved with Vecuronium 0.1 mg/kg intravenous. Minimal monitoring was adhered, basal haemodynamic parameters (heart rate, SBP, DBP and MAP) were recorded preoperatively and at 1, 3, 5 and 10 min post intubation and at extubation.

The values were represented in Number, (%) and Mean±SD. The statistical methods used were Chi(χ^2)square test, Student 't' test, paired 't' test, Mann-Whitney U test and Wilcoxon Signed Rank Statistic W+. The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software.

Result

A total of 60 patients of ASA Grade I and II were included in the study, divided in two equal groups. The demography of studied population was evenly distributed for their age, height, weight, BMI and gender, distribution was statistically non-significant ($p>0.05$) (Table 1) (Fig -1). The baseline hemodynamic variables i.e. heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure of either group were identical, distributed around respective Means and their SDs. Their distribution was statistically not significant ($p>0.05$) (Table 2) (Fig -2).

The heart rate immediately after intubation at 0-min was higher in Group I compared to Group II and it was statistically significant ($p<0.001$), while at 1, 3, 5,10 post-intubation and 2 min after extubation periods heart rate of Group II remained higher than that of Group I, but their difference was statistically not significant(Table 3) (Fig -1). The systolic blood pressure immediately at 0 -1 min post intubation was higher in Group I compared to Group II and it was statistically significant ($p<0.001$), while at induction, 3, 5,10 post-intubation and 2 min after extubation periods systolic blood pressure in Group I and II remained similar and statistically non-significant (Table 4) (Fig -2). The diastolic blood pressure in either group remained unchanged except two statistical aberration showing significant lower recording of DBP at induction and a higher recording at 1 minute post intubation (Table 5) (Fig - 3). There was a statistically significant fall in mean arterial pressure at induction in Group I, but at subsequent recording at 0 and 1min the MAP recorded a significant fall in Group II (Table 6) (Fig - 4).

The intra group comparisons of heart rate, SBP, DBP and MAP in either Group I and Group II, were the most significant observation. There was a statistically significant attenuation form base line in all the parameters recorded for either group at all time intervals, but there was not significant attenuation in DBP and MAP at induction in Group II (Fentanyl) and at 5 min post intubation in Group I (Dexmedetomidine). However after 10 min of intubation there was not significant attenuation of haemodynamic parameter in Group II (Fentanyl), but there was persistent and statistically significant haemodynamic attenuation in Group I (Dexmedetomidine) ($p>0.05$) (Table 7). Even, 2 minutes after extubation the haemodynamic parameters in Group I (Dexmedetomidine) remained attenuated, but there was no attenuation of haemodynamic parameters in Group II (Fentanyl). Even, 2 minutes after extubation the haemodynamic parameters in Group I (Dexmedetomidine) remained attenuated, but there was no attenuation of haemodynamic parameters in Group II (Fentanyl).

The was no significant difference in Aldrete scoring, observed at 10 min, however the request for rescue analgesic was earlier in Group II (Fentanyl), and it was statistically significant for Group I. There was a higher incidence of PONV in Group II, but in comparison it was statistically not significant.

Table 1: Demographic Variables

Sr. No.	Demographic (Variables) (N=60)	Group I Dexmedetomidine (n=30)		Group II Fentanyl (n=30)	
		Mean	SD	Mean	SD
1	Age (year)	35.65	11.13	37.45	10.90
2	Height (m)	1.59	0.08	1.60	0.06
3	Weight (kg)	64.15	5.95	64.63	5.72
4	BMI (kg/m^2)	25.24	3.48	25.13	1.72
5	Male	25	77.5%	24	70.0%
6	Female	5	22.5%	6	30.0%

Table 2: Inter Group Comparison of Baseline Hemodynamic Variables

Variables	Group I (n=30)		Group II (n=30)		Statistical significance	
	Mean	SD	Mean	SD	't'	'p'
Heart rate	76.17	7.08	77.93	7.32	-1.344	0.182
Systolic Blood Pressure	127.20	8.87	127.20	11.03	0.000	1.000
Diastolic Blood Pressure	72.60	5.42	74.10	4.14	-1.704	0.091
Mean arterial pressure	90.74	6.20	91.81	5.13	-1.030	0.305

Table 3: Inter Group Comparison of Heart Rate

Time intervals	Group I (n=30)		Group II (n=30)		Statistical significance	
	Mean	SD	Mean	SD	't'	'p'
Baseline	76.17	7.08	77.93	7.32	-1.344	0.182
At induction	80.70	10.54	81.80	8.06	-0.642	0.522
0 min post-intub	92.07	9.22	83.80	10.46	4.593	**<0.001**
1 min post-intub	90.10	7.09	87.15	12.55	1.585	0.116
3 min post-intub	85.40	5.67	87.00	10.74	-1.020	0.310
5 min post-intub	80.60	5.78	81.20	8.71	-0.445	0.657
10 min post-intub	75.80	4.81	78.00	7.27	-1.954	0.053
2 min post-extubation	85.34	5.58	86.78	10.72	-1.018	0.309

Table 4: Inter Group Comparison of Systolic Blood Pressure

Time intervals	Group I (n=30)		Group II (n=30)		Statistical significance	
	Mean	SD	Mean	SD	't'	'p'
Baseline	127.20	8.87	127.20	11.03	0.000	1.000
At induction	111.70	8.94	128.05	10.59	-9.141	**<0.001**
0 min post-intubation	142.90	7.40	135.60	11.40	4.162	**<0.001**
1 min post-intubation	146.60	6.38	138.20	11.38	4.987	**<0.001**
3 min post-intubation	134.20	6.56	136.25	12.39	-1.132	0.260
5 min post-intubation	128.80	5.35	129.40	10.15	-0.405	0.686
10 min post-intubation	129.60	4.58	124.45	10.65	3.442	0.001
2 min post-extubation	134.12	6.55	136.19	12.29	-1.131	0.256

Table 5: Inter Group Comparison of Diastolic Blood Pressure

Time intervals	Group I (n=30)		Group II (n=30)		Statistical significance	
	Mean	SD	Mean	SD	't'	'p'
Baseline	72.60	5.42	74.10	4.14	-1.704	0.091
At induction	65.60	5.09	75.00	3.45	-11.848	**<0.001**
0 min post-intubation	83.30	6.13	79.40	5.81	3.579	0.001
1 min post-intubation	89.60	3.91	79.75	4.03	13.583	**<0.001**
3 min post-intubation	78.40	6.86	79.30	4.22	-0.866	0.388
5 min post-intubation	73.50	5.41	76.30	4.05	-3.211	0.002
10 min post-intubation	76.90	5.86	74.55	3.79	2.607	0.010
2 min post-extubation	78.36	6.73	79.16	4.16	-0.742	0.277

Table 6: Inter Group Comparison of Mean Arterial Pressure

Time intervals	Group I (n=30)		Group II (n=30)		Statistical significance	
	Mean	SD	Mean	SD	't'	'p'
Baseline	90.74	6.20	91.81	5.13	-1.030	0.305
At induction	80.91	6.33	92.92	4.83	-11.690	**<0.001**
0 min post-intubation	103.10	6.32	97.92	5.85	4.658	**<0.001**
1 min post-intubation	108.70	4.20	99.23	5.26	10.906	**<0.001**
3 min post-intubation	97.05	6.75	98.45	5.94	-1.207	0.230
5 min post-intubation	91.90	4.45	94.05	5.11	-2.464	0.015
10 min post-intubation	94.47	5.26	90.95	5.17	3.694	**<0.001**
2 min post-extubation	97.03	6.66	98.21	5.86	-1.203	0.212

Table 7: Intra & Inter Group Statistical Significance (p-Value)

Time Interval	Group I				Group II			
	Heart rate	SBP	DBP	MAP	Heart rate	SBP	DBP	MAP
At induction	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.008**	0.276	0.056
0 min post-intubation	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
1 min post-intubation	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
3 min post-intubation	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
5 min post-intubation	**<0.001**	**0.008**	0.285	0.095	**0.005**	**0.008**	**0.006**	**0.006**
10 min post-intubation	**0.005**	**0.006**	**0.006**	**<0.001**	0.810	0.280	0.122	0.145
2 min post-extubation	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.450	0.164	0.253	0.243

Table 8: Recovery Characteristics

Parameters	Group I	Group II	p-Value
Aldrete Score at 10 min	09	08	p-Value: 0.2265 t-Value: -1.225
Rescue Analgesic (Mean)	80	72	**p-Value: 0.006** t-Value: -2.805
PONV	05(16.66%)	09(30%)	p-Value: 0.0359 t-Value: 2.148

Fig -1

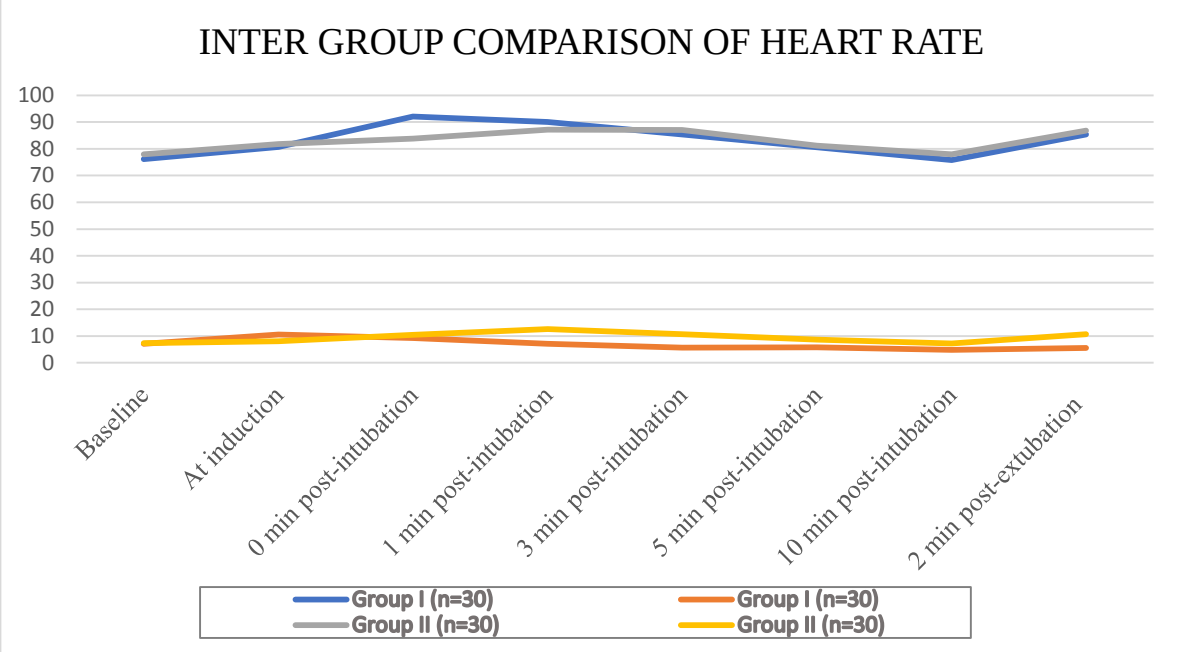


Fig –2

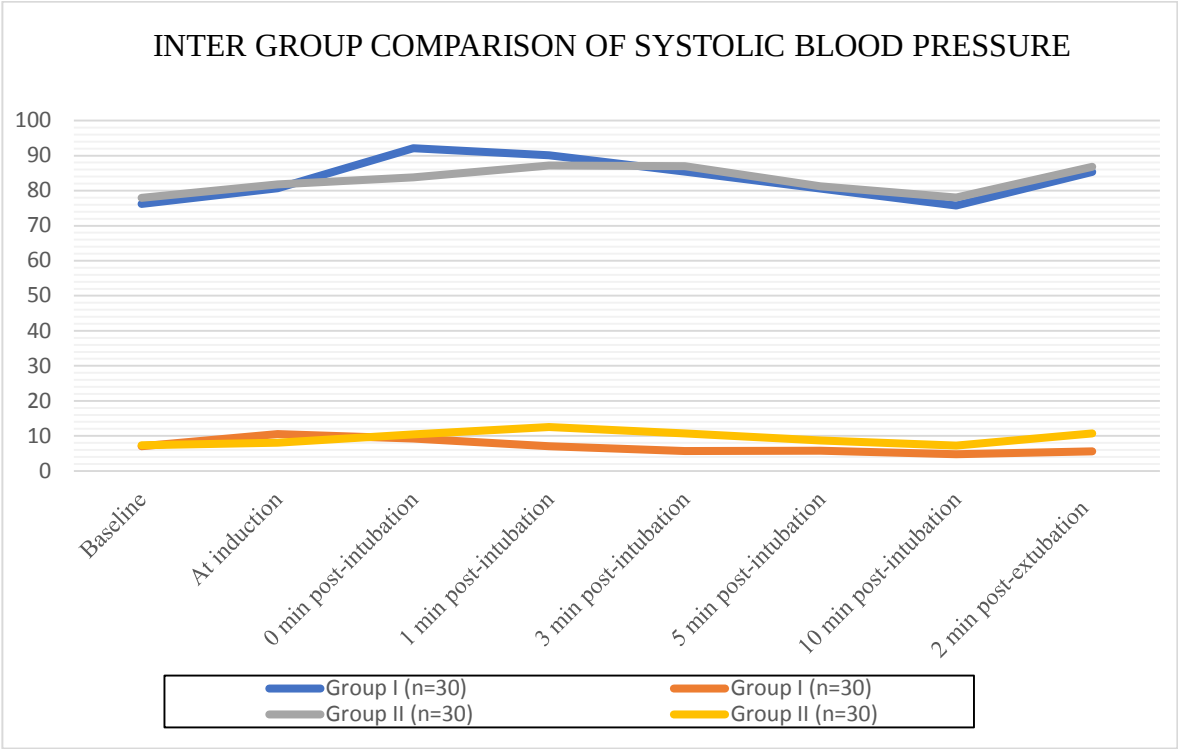

INTER GROUP COMPARISON OF SYSTOLIC BLOOD PRESSURE
100
90
80
70
60
50
40
30
20
10
0
Baseline
At induction
0 min post-intubation
1 min post-intubation
3 min post-intubation
5 min post-intubation
10 min post-intubation
2 min post-extubation
Group I (n=30)
Group I (n=30)
Group II (n=30)
Group II (n=30)

Fig –3

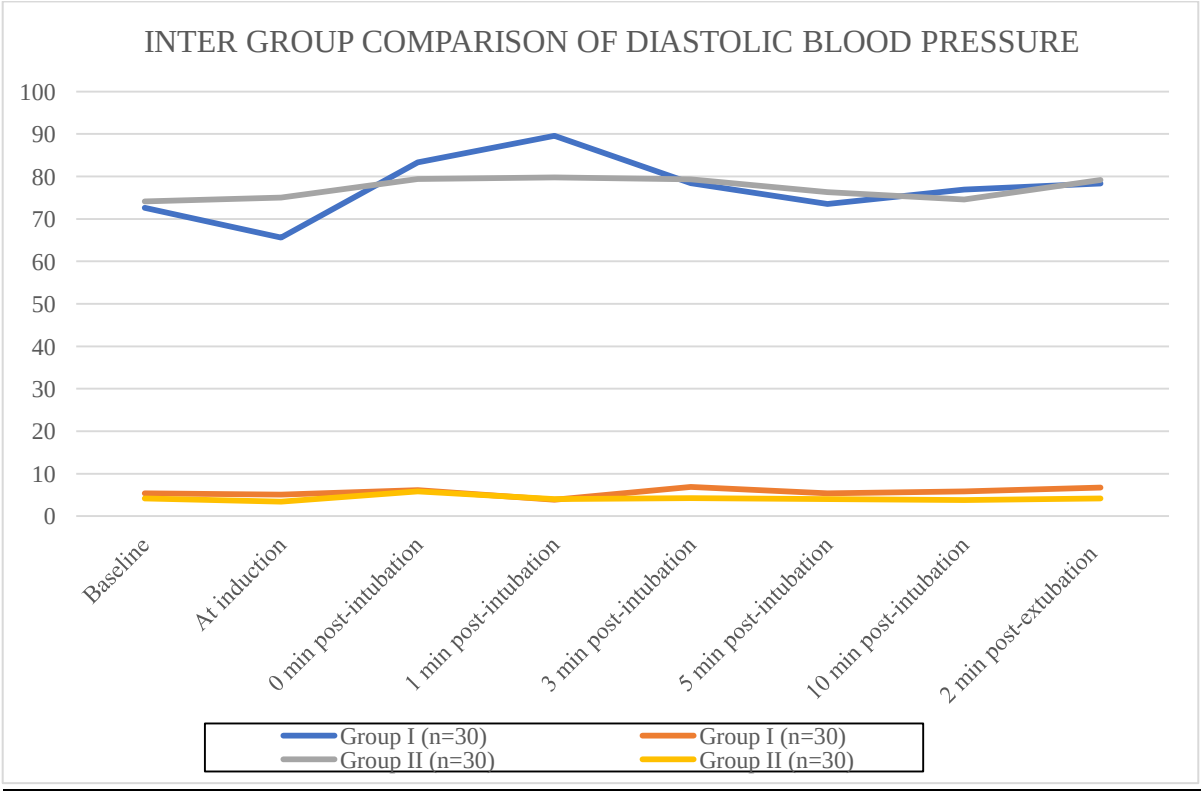
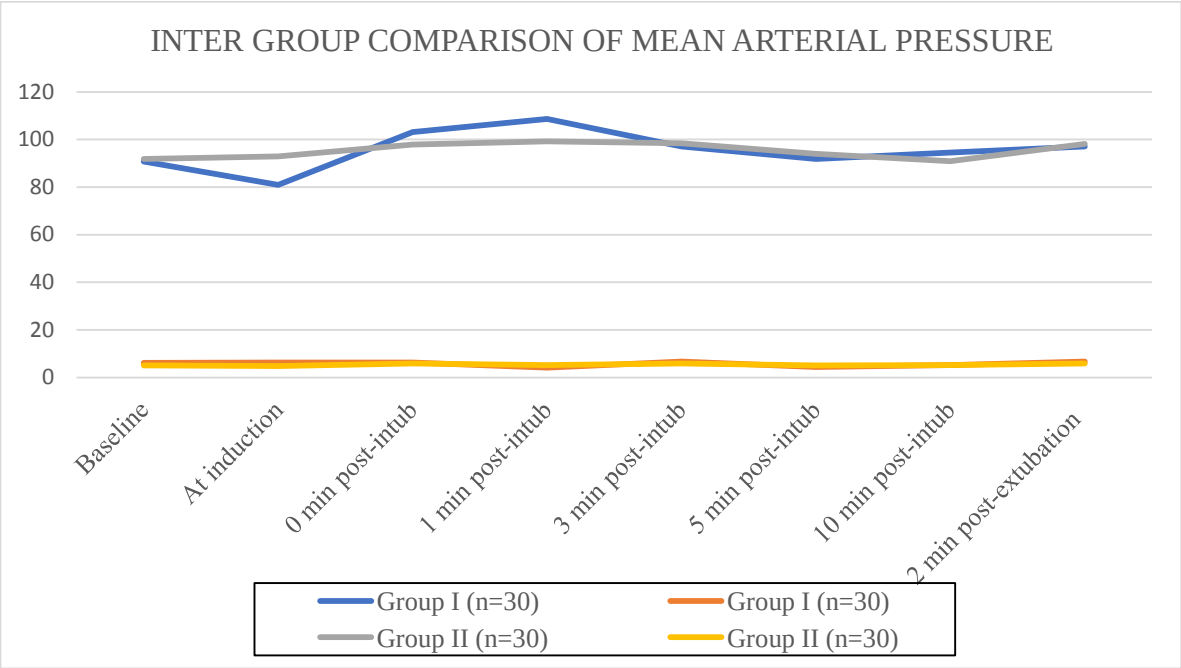

INTER GROUP COMPARISON OF DIASTOLIC BLOOD PRESSURE
100
90
80
70
60
50
40
30
20
10
0
Baseline
At induction
0 min post-intubation
1 min post-intubation
3 min post-intubation
5 min post-intubation
10 min post-intubation
2 min post-extubation
Group I (n=30)
Group I (n=30)
Group II (n=30)
Group II (n=30)

Fig - 4



Discussion

Transient haemodynamic surge following laryngoscopy and intubation is critical cardiovascular stress, attributed to increased catecholamine following sympathoadrenal discharge caused by epipharyngeal and parapharyngeal stimulations that eventually results in increase in heart rate (20%), blood pressure (45-50%), myocardial oxygen demand, and dysrhythmias.[1,5,13]. The modalities tried to attenuate this pressure response has targeted both the afferent (smooth and swift laryngoscopy, deeper plane of anaesthesia, increased MAC for volatile inhalational agents, topical lignocaine spray and intravenous opioids) as well as efferent limb (anti hypertensives, β-blockers, calcium channel blockers, vasodilators and adrenergic blockers).[14]

This was a prospective, randomized, double blind, comparative study, undertaken to determine and compare the efficacy of dexmedetomidine and fentanyl in attenuating the pressor response to laryngoscopy and intubation and effects on analgesia. The two groups were matched demographically for age, height, weight, BMI and gender distribution and baseline hemodynamics, thus showing no confounding effect of these variables.

The α2 adrenoceptors are ubiquitous in their distribution and are located primarily in the locus ceruleus, spinal cord, and autonomic nerves. Dexmedetomidine an α_2-adrenergic receptor agonist, exerts its effects on numerous organ systems by its action on α adrenoceptors and its three subtypes: α2A, α2B, and α2C. Depending on the specific receptor that is activated, α2 agonists may cause hypotension, bradycardia, sedation, analgesia, attenuation of shivering, and attenuation of haemodynamic responses[15]. In present study dexmedetomidine initiated with a loading dose of 1 µg/kg intravenous and a maintenance dose of 0.4 µg/kg/hr, unlike other studies where a higher dose of continuous intravenous infusion (0.7 - 10 µg/kg/hr) was associated with significant bradycardia and hypotension.[16] There was a transient increase in HR, SBP, DBP and MAP initially during dexmedetomidine infusion, followed by a decrease in these parameters probably due to the vasoconstrictive effect of dexmedetomidine appearing earlier than the central sympathetic action, similar to earlier studies[17].

The concept of high-dose opioid anaesthesia Lowenstein et al widely popularised the intraoperative use of fentanyl alone and in several combinations, since its introduction by Dr. Paul Janssen in the late 1950.[18,19]. Intravenous bolus dose of fentanyl 2 µg /kg administered 5 min before induction has been found to be the most effective in attenuating the hemodynamic response to intubation[20]. It has further been suggested that co-administration of a small dose of fentanyl, before the induction suppresses the hemodynamic response to endotracheal intubation more than it suppresses the response to laryngoscopy.[21] Addition of 2 µg fentanyl intravenous bolus to 1 MAC sevoflurane anaesthesia at induction attenuated the hemodynamic response to a maximum of 15% above baseline values.[22] There has been reports on inconsistent effects of Fentanyl on haemodynamics, when a bolus dose of 2µg/kg intravenous administered ten minutes prior to airway instrumentation, the increase in SBP, DBP, MAP and heart rate were above baseline levels after airway instrumentation.[14]

In present study the core concerns of intraoperative inconsistent haemodynamic response to perioperative events like induction, intubation, intraoperative surgical instrumentation and extubation were addressed. The perioperative period was supplemented with a bolus pre-induction doses of dexmedetomidine and fentanyl to respective group and an infusion of the same drug was continued till extubation. The intraoperative haemodynamics remained significantly attenuated, without any inconsistent recordings and within limits. Either group has shown significant attenuation, however the dexmedetomidine group showed better perioperative haemodynamic attenuation, longer analgesia and better recovery. The common adverse effects of dexmedetomidine and fentanyl include hypotension, bradycardia, respiratory depression, nausea and PONV, mostly attributable to their dose schedules were not minimal and non-significant.

Conclusion

The current study concludes that blood pressure (SBP, DBP, and MAP) and heart rate following laryngoscopy and endotracheal intubation are a critical perioperative event, smooth attenuated control of these parameters are of paramount importance particularly in co-morbid conditions. These variables were significantly addressed in present study and it was concluded that a bolus supplemented with continuous infusion of both dexmedetomidine and fentanyl are nearly competitive in attenuation of haemodynamics without compromising patient safety and recovery from anaesthesia.

Abbreviation

ASA: American Society of Anaesthesiologists, BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, GA: General Anaesthesia. PONV: Post-Operative Nausea and Vomiting.

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