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CLINICAL COMPARISON OF COINDUCTION FENTANYL V/S MIDAZOLAM

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ABSTRACT

Term Coinduction of Anaesthesia is applied to the use of two or more drugs to induce anaesthesia. This study is taken up to evaluate clinically Fentanyl v/s Midazolam for Coinduction.60 Patients of ASA grade I & II are included in this study & are divided into three groups. Group A are patients receiving Fentanyl, Group B are patients receiving Midazolam for coinduction and Group C is the control group. Induction time is maximum in Fentanyl group. Dose of Thiopentone Sodium required is minimum in Fentanyl group. Evidence of nausea is minimum in Midazolam group. Calming down is shortest in Midazolam group. After giving the two drugs in their respective groups pulse rate was significantly increased in Midazolam group, while there is no significant difference in Systolic & Diastolic BP in this study. For clinical comparison of coinduction Fentanyl is better than Midazolam.

KEY WORDS: *Induction Time, Calming Down (Sedation Time), Post operative Nausea, Fentanyl, Midazolam, Thiopentone Sodium.*

INTRODUCTION:

The term coinduction of anaesthesia has been applied to the use of two or more drugs to induce anaesthesia. The term was introduced in 1986 to describe the unplanned induction of anaesthesia. Currently planned induction of anaesthesia is practised by anaesthetists exploiting drug interaction, particularly synergism, principally between Midazolam, Fentanyl, Sufentanyl, Propofol etc. It can produce an improvement in all phases of anaesthesia including Induction Maintenance & Recovery. (Whitwam JG. 1995)[1]

Barbiturates (commonly Thiopentone Sodium) are the commonly used intravenous induction agents. They depress the Reticulo endothelial activated system (RAS). Benzodiazepines eg Midazolam belongs to a new class of Imidazo-benzodiazepines. Due to its cardiovascular stability, amnesic & anxiolytic properties it has found particular usefulness in poor risk elderly cardiac patients. Opioids eg Fentanyl, the first of the 4-anilinopiperidine series of opiate agonists is a chemical congener of the revised ester of Pethidine & is 75-125 times more potent than Morphine.

MATERIAL & METHODS:

After approval by institutional ethical committee & written informed consent 60 adult surgical patients of ASA Grade I & II with ± 20% of ideal body weight & of either sex between 15-70 years age were included in the study. Patients were divided into three groups. Patients in all the three groups received Injection Glycopyrrolate 0.2 mg. I/V and Injection Tramadol 100 mg I/V.

Group A: Patients induced with Fentanyl (2µg/ kg.I/V) & Thiopentone Sodium (dose as required) & then intubated with Succinylcholine (2mg/ kg.I/V)

Group B: Patient induced with Midazolam (.03-.3 mg/ kg. I/V) & Thiopentone sodium (dose as required) & then intubated with Succinylcholine (2mg/ kg. I/V)

Group C: Patient induced with Thiopentone Sodium (5 – 7 mg/ kg. I/V) & then intubated with Succinylcholine (2mg/ kg. I/V)

Technique of Anaesthesia: Pre operative Preparation: nil orally for 6 hrs prior to induction of anaesthesia.

Anaesthetic sequence:

a) Pre-oxygenate using 100% oxygen for 3 minutes
b) Patients in all three groups received glycopyrrolate 0.2mg I/V and Injection Tramadol 100 mg I/V and were induced & intubated with respective agents using appropriate size cuffed endotracheal tube.
c) Anaesthesia was maintained on Oxygen, Nitrous Oxide, Injection Vecuronium & IPPR.

Patients were continuously monitored & following parameters were recorded.

1. Pulse rate
2. BP (both systolic & diastolic in mm of Hg)
3. Calming down or sedation time with Fentanyl & Midazolam.
4. Dose of Thiopentone Sodium required.
5. Induction time – with loss of eyelash reflex (after giving Thiopentone Sodium)
6. Nausea, Vomiting & difficulty in breathing in the post operative period.

Pulse rate & BP were recorded during following stages of Anaesthesia.

1. Before giving Glycopyrrolate as premedication.
2. 2 minutes after giving Fentanyl or Midazolam.
3. After giving Thiopentone Sodium.
4. At every 1 minute interval after intubating the patient till first 5 minutes.
5. At every 5 minutes interval for next 10 minutes.
6. At 15 minutes interval after the last reading.

Statistical analysis was done using ‘t’ test, Chi square & ‘p’ values.

OBSERVATIONS:

Induction time is maximum in the patients receiving Fentanyl, then in control group & minimum in the patients receiving Midazolam. Dose of Thiopentone Sodium required for induction is maximum in the control group, then in patients receiving Midazolam & minimum in patients receiving Fentanyl. (Tab-1)

Table -1 - Comparison of Induction Time & Doses of Thiopentone Sodium

	COMPARISON OF INDUCTION TIME		COMPARISON OF DOSES OF THIOPENTONE SODIUM	
COMPARISON	t	p	t	p
A vs B	2.1578	p<0.05	3.4236	<0.01
A vs C	2.7265	p<0.01	29.3399	<0.001
B vs C	0.3458	NS	15.4855	<0.001

Evidence of nausea in the postoperative period is maximum in patients receiving Fentanyl, then in control group & minimum in patients receiving Midazolam. (Tab-2)

Table – 2 - Comparison of Nausea vomiting among the groups

		A		**B**		**C**	
		No.	%	No.	%	No.	%
ANALYSIS OF NAUSEA AMONG THE GROUPS	P	15	75	5	25	7	35
	A	5	25	15	75	13	65
	TOTAL	20	100	20	100	20	100
ANALYSIS OF VOMITING AMONG THE GROUPS	P	3	15	0	-	1	5
	A	17	85	20	100	19	95
	TOTAL	20	100	20	100	20	100
ANALYSIS OF DIFFICULTY IN BREATHING AMONG THE GROUPS	P	-	-	-	-	-	-
	A	20	100	20	100	20	100
	TOTAL	20	100	20	100	20	100

Calming down (Sedation time), when Fentanyl is compared to Midazolam is significantly increased in patients receiving Fentanyl than in patients receiving Midazolam. (Tab-3)

Table -3 - Comparison of calming down

ANALYSIS OF CALMING DOWN AMONG THE GROUPS				
	A (Mean ± SD)	B (Mean ± SD)	't'	'p'
CALMING DOWN	66.75± 10.41	46.75± 9.49	6.3496	< 0.001

After giving the drugs Fentanyl & Midazolam in the respective groups, pulse rate was significantly increased in the groups receiving Midazolam, while there is no significant difference in the systolic & Diastolic BP in this study. After giving Thiopentone Sodium but before intubation pulse rate is maximum in the control group, then in the group receiving Midazolam & minimum in the group receiving Fentanyl. Fall in systolic & diastolic BP is minimum in patients receiving Fentanyl, then in patients receiving Midazolam & maximum in control group. Systolic & Diastolic BP reading have fallen below the baseline values both in Fentanyl & Midazolam groups. However, this fall is more pronounced in Midazolam group. In our study of 60 patients no specific management was required for the fall in Systolic and Diastolic BP and neither did it have any deliterious effect.

For 5 minutes after intubation ie, 1,2,3,4 & 5 minutes after intubation, pulse rate, systolic & Diastolic BP all are maximally increased in the control group, then in the group receiving Midazolam & minimum in the group receiving Fentanyl. All the values are above the baseline:

10, 15 & 30 minutes after intubation- Pulse rate, Systolic & Diastolic BP all are maximally increased in the control group, then in the group receiving Midazolam & minimum in the group receiving Fentanyl. The values of Systolic & Diastolic BP in groups receiving Fentanyl & Midazolam are below the baseline values. In our study of 60 patients mean Systolic BP in Midazolam group was around 125 mmHg and it came down to 117 mmHg 30 minutes after intubation, while mean Systolic BP in Fentanyl group was around 122 mmHg and it came down to 115 mmHg 30 minutes after intubation. Mean Diastolic BPin Midazolam group was around 81 mmHg and it came down to 79 mmHg 30 minutes after intubation, while mean Diastolic BP in Fentanyl group was 80 mmHg and it came down to 77 mmHg 30 minutes after intubation.(Tab – 4,5,6) (Fig – 1,2,3)

Table – 4 - Analysis of pulse rate among the groups

ANALYSIS OF PULSE RATE (BEATS / MINUTE)												
Group		**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**	**X**	**XI**
A	Pulse Rate (N=20) (Mean± SD)	86.4± 8.66	80.7± 6.46	87.5± 6.52	114.5± 6.98	110.75± 7.44	104.6± 7.05	94.6± 20.16	94.7± 10.64	86.8± 6.33	83.6± 4.84	77.7± 4.99
	Change (Mean±SD)	-	-5.7 ± 3.96	1.1 ± 1.05	28.1 ± 5.49	24.35 ± 6.55	18.2 ± 8.41	8.2 ± 11.23	8.3 ± 12.84	0.4 ± 8.69	- 2.8 ± 7.88	- 8.7 ± 6.33
	t		6.4772	4.7142	23.032	16.7290	9.7384	3.2858	2.9088	0.2071	1.5418	6.1848
	p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.01	<0.01	NS	NS	<0.001
B	Pulse Rate (N=20) (Mean± SD)	91.00± 7.19	87.6± 7.39	96.4± 7.39	124.1± 3.92	123.7± 5.18	116.3± 5.74	109.4± 6.78	104.1± 7.57	94.7± 9.21	90.4± 6.74	84.6± 5.06
	Change (Mean±SD)	-	-3.4± 3.29	5.4± 3.29	33.1± 7.60	32.7± 8.01	25.3± 7.62	18.4± 9.60	13.1± 10.28	3.7± 10.39	-0.6± 8.87	-6.4± 7.30
	t		4.6504	7.386	19.5986	18.3707	14.9409	8.625	5.7344	1.6025	0.3043	3.9452
	p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	NS	NS	<0.001
C	Pulse Rate (N=20) (Mean± SD)	83.3± 11.59		91.9± 9.62	127.0± 6.65	126.8± 6.01	123.9± 6.46	119.5±6.78	115.95± 6.41	103.9± 6.24	97.35± 5.37	91.0± 6.43
	Change (Mean±SD)	-		8.6± 3.37	43.7± 8.72	43.45± 8.21	40.6± 8.17	36.2± 8.46	32.8± 8.69	20.6± 10.1	14.05± 9.20	7.70± 7.93
	t			11.4836	22.5516	23.8154	22.3623	19.2553	16.985	9.1782	6.8732	4.3694
	p			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table- 5 – Analysis of Systolic BP among the groups

ANALYSIS OF SYSTOLIC BP (mm Hg.)												
Group		I	II	III	IV	V	VI	VII	VIII	IX	X	XI
A	Systolic BP (Mean±SD)	122.6± 8.22	119.3± 7.33	114.0± 7.36	140.15± 6.15	137.55± 6.28	130.75± 6.10	126.7± 6.49	123.55± 6.69	119.4± 5.44	117.6± 4.84	115.3± 5.45
	Change (Mean±SD)	-	-3.3± 2.70	-8.6± 3.2	17.55± 6.17	14.95± 7.02	8.15± 7.72	4.1± 8.61	0.95± 8.14	-3.2± 8.79	-5.0± 7.28	-7.3± 7.13
	t		5.5000	12.093	12.7998	9.5833	4.7506	2.1428	0.5257	1.6382	3.1120	4.6073
	P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.05	NS	NS	<0.01	<0.001
B	Systolic BP (Mean±SD)	125.1± 6.19	120.4± 7.26	111.6± 7.26	146.2± 6.56	141.1± 8.84	133.9± 9.08	130.4± 8.89	127.3± 8.53	122.2± 5.33	120.2± 5.75	117.3± 7.02
	Change (Mean±SD)	-	-4.7± 3.36	-13.5± 3.36	21.1± 6.04	16.0± 8.34	8.8± 9.11	5.3± 10.39	2.20± 10.46	-2.90± 8.06	-4.9± 8.29	-7.8± 9.82
	t		6.2946	18.080	15.720	8.6331	4.3468	2.2954	0.9464	1.6191	2.6598	3.5562
	P		<0.001	<0.001	<0.001	<0.001	<0.001	<0.05	NS	NS	<0.05	<0.01
C	Systolic BP (Mean±SD)	119.9± 11.53		10.35± 10.23	159.0± 8.43	158± 8.58	154.0± 8.29	148.8± 8.42	144.9± 8.88	133.9± 10.2	130.1± 9.44	126.3± 7.65
	Change (Mean±SD)	-		-16.4± 2.73	39.1± 9.86	38.1± 9.62	34.1± 9.02	28.9± 9.75	25.0± 10.98	14.0± 10.0	10.1± 9.86	6.40± 8.76
	t			27.033	18.7981	17.8224	17.012	13.3384	10.2459	6.3000	4.6095	3.2876
	P			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.01

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Table- 6 -Analysis of Diastolic BP among the groups **ANALYSIS OF DIASTOLIC BP (mm Hg.)**

Group		I	II	III	IV	V	VI	VII	VIII	IX	X	XI
A	Diastolic BP Mean±SD)	80.0 ± 4.77	78.6± 4.05	77.2± 4.27	98.1± 4.07	95.05± 3.39	87.95± 3.77	85.55± 4.77	83.8± 6.32	79.9± 3.60	78.8± 3.66	77.0± 4.87
	Change (Mean±SD)	-	-1.4± 2.37	-2.8± 1.27	18.1± 4.07	15.05± 3.78	7.95± 3.93	5.55± 5.22	3.8± 6.98	-0.1± 3.65	-1.2± 4.12	-3.0± 4.84
	't'		2.6582	9.9213	20.0122	17.9167	9.1031	9.7844	2.4498	0.1232	1.3106	2.7892
	'p'		<0.05	<0.001	<0.001	<0.001	<0.001	<0.001	<0.05	NS	NS	<0.01
B	Diastolic BP Mean±SD)	81.6 ± 5.04	79.7± 4.11	74.7± 4.11	99.3± 2.55	97.1± 2.93	91.7± 4.74	86.9± 4.87	85.6± 4.45	81.5± 4.81	81.0± 3.55	79.7± 2.12
	Change (Mean±SD)	-	-1.9± 2.12	-4.2± 1.74	17.7± 5.26	15.5± 5.26	10.1± 7.45	5.30± 7.65	4.0± 7.12	0.90± 7.33	-0.6± 5.62	-1.9± 5.27
	't'		4.0330	10.8620	15.1425	13.260	6.092	3.1176	2.5281	0.5525	0.4804	1.6223
	'p'		<0.001	<0.001	<0.001	<0.001	<0.001	<0.01	<0.05	NS	NS	NS
C	Diastolic BP Mean±SD)	77.9 ± 6.71		72.1± 5.51	109.3± 4.53	108.3± 3.86	104.7± 5.18	99.1± 4.40	96.0± 4.60	89.5± 3.34	86.3± 3.96	84.2± 4.33
	Change (Mean±SD)	-		-5.8± 1.62	31.4± 5.41	30.4± 5.92	26.8± 6.71	21.2± 5.49	18.1± 6.46	11.6± 6.77	8.40± 5.49	6.3± 6.21
	't'			16.111	26.1182	23.1081	17.9731	17.3770	12.6083	7.7105	6.8852	4.5652
	'p'			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

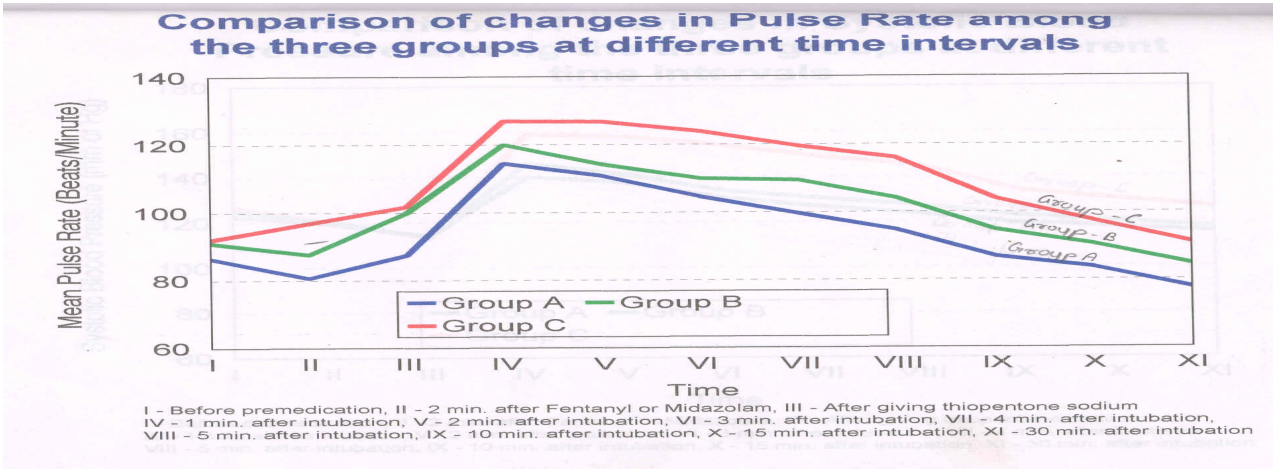

Figure – 1 Comparison of changes in pulse rate among the three groups at different time intervals

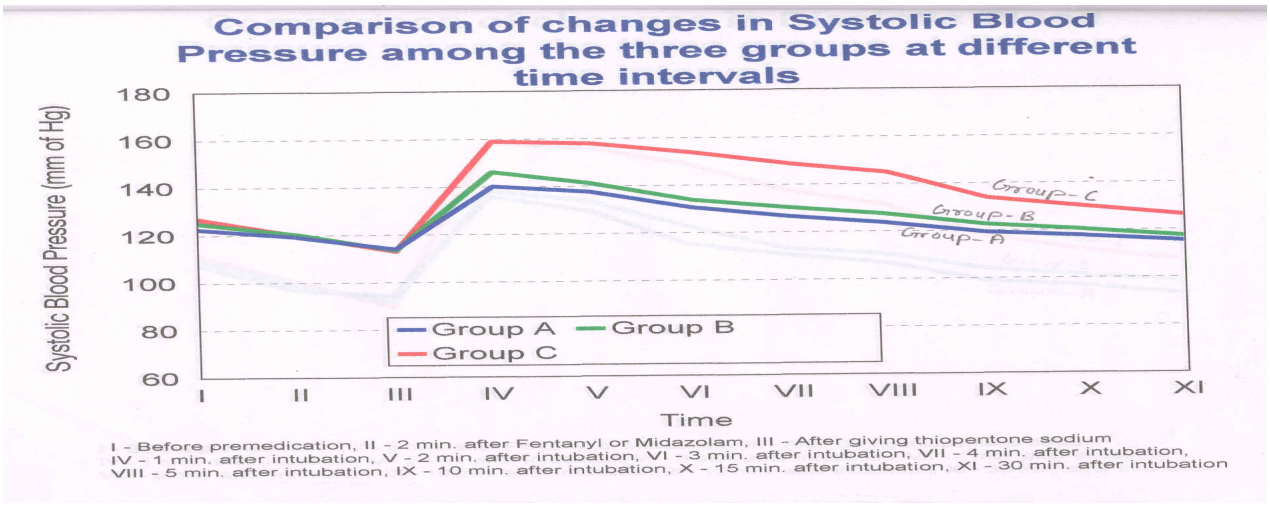

Figure -2 Comparison of changes in systolic blood pressure among the three groups at different time intervals

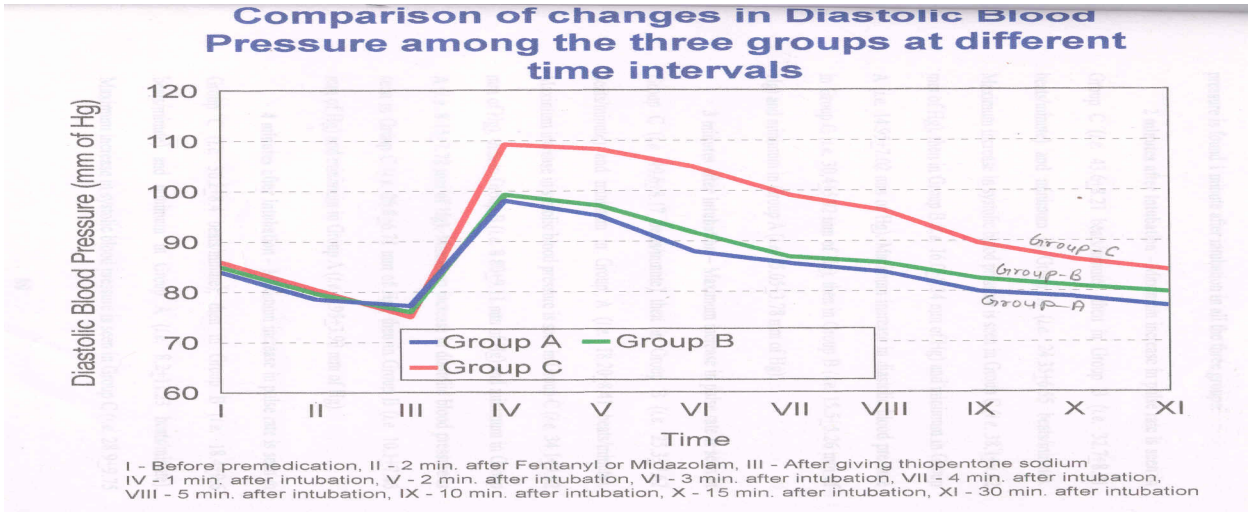

Figure -3 Comparison of changes in diastolic blood pressure among the three groups at different time intervals

DISCUSSION:

Our findings corroborated with Frances Chung & David Evans in 1985, who conducted a study to determine whether the use of Fentanyl during induction would attenuate the cardiovascular response to laryngoscopy & intubation. They concluded Fentanyl as an adjunct to Barbiturate induction effectively lowered Thiopentone requirement & attenuated the pressor response to laryngoscopy & intubation. (Frances Chung & David Evans 1985)[2]

In our study we did not come across any disturbances in cardiac rhythm. More pronounced stable hemodynamics was observed with Fentanyl than Midazolam.

Short et al (1991)[3] studied the effects of Thiopentone & Midazolam alone and in combination for hypnosis a synergistic interaction was found. The dose of Thiopentone required to produce anaesthesia was reduced by 50% in presence of Midazolam. This is also seen in our study of 60 patients. The dose of Thiopentone Sodium required in Midazolam group is 213.50 ± 24.98 in comparison to 300.0± 0.00 in control group.

The incidence of post operative emergence delirium, nausea & vomiting is relatively low following Midazolam administration as compared with other anaesthetic agents. This is also seen in our study of 60 patients, 25% patients from Midazolam group suffered from post operative nausea while in control grooup percentage was 35% and 75% in patient receiving Fentanyl.

According to Lunn et al (1979) intravenous Fentanyl & Alfentanyl in high doses successfully suppressed stress response to intubation (Lunn et al 1979)[4] Kautto UM (1982)[5] concluded that Fentanyl supplementation with 2µg/ kg significantly attenuated arterial pressure & heart rate increase during laryngoscopy & intubation & Fentanyl 6 µg/ kg completely abolished these responses. Dahlgren et al (1981)[6] conclued that Fentanyl treatment caused a significant attenuation of the blood pressure & pulse response to laryngoscopy & intubation.

This is also seen in our study as the increase in pulse rate, Systolic and Diastolic BP is maximum 1 minute after intubation in all the three groups & it decreases thereafter. Among the three groups these vitals are maximum in the control group, then in the group receiving Midazolam & minimum in the group receiving Fentanyl.

Opioids have a unique role as anaesthetic agents in patients with minimal cardiovascular reserve. Anaesthesia which can provide attenuation of the hormonal & metabolic responses to surgery (Hall, 1980)[7] in a technique so called Stress Free Anaesthesia. Histamine release is rare with Fentanyl (Yee et al & Calis et al, 1992).[8&9] This also contributed to the cardiovascular stability it offers.

Sebel et al (1982)[10] concluded the lack of cardiovascular depression produced by Fentanyl and its ability to reduce hormonal & metabolic responses to surgery make it a satisfactory technique for cardiac anaesthesia. This is also seen in our study as the increase in pulse rate, Systolic and Diastolic BP is maximum 1 minute after intubation in all the three groups & it decreases thereafter. Among the three groups these vitals are maximum in the control group, then in the group receiving Midazolam & minimum in the group receiving Fentanyl.

Fentanyl shares the toxic potential of Opioids when compared with other Opioids. Fentanyl has lower incidence of nausea, vomiting & pruritis, however Bradycardia, hypotension, skeletal muscle rigidity, laryngospasm, bronchoconstriction can occur. In our study also evidence of nausea & vomiting is seen. 75% patients receiving

Fentanyl suffered from post operative nausea though percentage was 35% in control group and 25% in Midazolam group.

On comparison with the control group it is found that agents of induction do contribute a lot in stabilizing the hemodynamics of the patient. A combination of various anaesthetic agents & their hemodynamic effects when equated with patients condition are able to provide a good resultant effect in stabilizing hemodynamic.

RESULT:

From the present study we conclude

1. Induction time is maximum in the patients receiving Fentanyl, then in control group & minimum in the patients receiving Midazolam. (Tab-1)
2. Dose of Thiopentone Sodium required for induction is maximum in the control group, then in the patients receiving Midazolam & minimum in patients receiving Fentanyl. (Tab-1)
3. Evidence of nausea in the post operative period is maximum in patients receiving Fentanyl, then in the control group & minimum in patients receiving Midazolam. (Tab-2)
4. Calming Down (Sedation Time) when Fentanyl is compared to Midazolam is significantly increased in patients receiving Fentanyl then in patients receiving Midazolam. (Tab-3)
5. After giving the drugs Fentanyl & Midazolam in the respective groups, pulse rate was significantly increased in the group receiving Midazolam, while there is no significant difference in the Systolic and Diastolic BP in this study.

CONCLUSION:

It may thus be concluded that for Coinduction Fentanyl is better than Midazolam.

BIBLIOGRAPHY:

1. Whitwam JG. Eur J Anaesthesiol suppl. 1995 Nov. 12:25–34.
2. Frances Chung & David Evans. Can Anaesth. Soc. J. 1985, 32(6): 622-8.
3. Short TG. et al. Brit Jr. Anesth. 1991; 66: 13-19 Cited from Fulsed Prod. Monogr, Ranbaxy Pharma Mktg. New Delhi.
4. Lum JK, Stanley TH, Eiscle J & Woodward A. High dose Fentanyl anaesthesia for coronary Artery Surgery: Plasma (F) conc. & cardiovascular responses. Anaesth. Analg 1979; 58:390.
5. Kautto UM, Attenuation of the circulatory response to laryngoscopy & intubation by Fentanyl Acta Anaesthesia Scand 1982 Jun; 26 (3): 217-21
6. Dahlgren N, Messeter K. Treatment of stress response to laryngoscopy & intubation with Fentanyl Anaesthesia 1981 Nov.; 36 (11) : 1022-6
7. Hall GM. Fentanyl and the metabolic response to surgery. British Journal of Anaesthesia 1980; 52:562
8. Yee LY, Lopez JR. Transdermal Fentanyl, Ann Pharmacother 1992; 26: 1393-1399
9. Calis KA, Kohler DR, Corso DM. Transdermally administered Fentanyl for pain management. Clin Pharma 1992, 11:22-36
10. Sebel PS, Bovill JG, Boekhorst RA, Rog N. Cardiovascular effects of high dose Fentanyl anaesthesia Acta Anaesthesia Scand 1982 Aug; 26 (4): 308-15.