High dose Fentanyl versus Multi-agent Combination Technique for Induction of Anaesthesia in patients undergoing Coronary Artery Bypass Graft Surgery: A Randomized Controlled Trial

A Dissertation submitted in partial fulfillment of

M. D. Branch X (Anaesthesiology) Degree Examination of The

TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI,

to be held in April 2012.

C E R T I F I C A T E

This is to certify that the dissertation entitled **'High dose Fentanyl versus Multi-agent Combination Technique for Induction of Anaesthesia in patients undergoing Coronary Artery Bypass Graft Surgery: A Randomized Controlled Trial'** is the bonafide original work of Dr. Mary Tina Rani Vaz G., towards the M.D. Branch-X (Anaesthesiology) Degree Examination of the Tamil Nadu Dr. M.G.R University, Chennai, to be held in April 2012.

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AIM

To compare two induction regimens, namely, High dose Fentanyl and Multi-agent Combination Technique in patients who are being anaesthetized for Coronary Artery Bypass Graft Surgery, with regards to haemodynamic stability, during induction and tracheal intubation.

OBJECTIVES

The objectives of this study are to compare the effects of High dose Fentanyl and Multi-agent Combination Technique (Low dose Fentanyl, Midazolam and Sevoflurane) during induction of Anaesthesia, in patients undergoing coronary artery bypass graft surgery, with regards to:

1. Haemodynamic Stability during induction and tracheal intubation (Primary Outcome)
2. Requirement of vasopressors or vasodilators till tracheal intubation (Primary Outcome)
3. Incidence of chest wall rigidity (Secondary Outcome), assessed by
    a. Ease of bag and mask ventilation
    b. Drop in saturation

INTRODUCTION

The Review of Literature will be discussed under the following topics-

- Epidemiology Coronary artery disease- Worldwide
- Prevalence of Coronary Heart Disease in India
- Pathogenesis of Coronary artery disease
- Coronary artery bypass graft surgery
- Anaesthesia for CABG
- Relevant Cardiac Physiology
- Role of the Anaesthesiologist in CABG
- Induction of Anaesthesia
- Haemodynamic responses during intubation
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- High dose fentanyl
- Justification for study
- Research question

LITERATURE REVIEW

Epidemiology of Coronary Artery Disease (1)

Cardiovascular disease is now the most common cause of death worldwide. Before 1900, infectious diseases and malnutrition were the most common causes of death throughout the world, and cardiovascular disease was responsible for <10% of all deaths. Today cardiovascular disease accounts for around 30% of deaths worldwide, including nearly 40% in high-income countries and about 28% in low- and middle-income countries.

The global rise in cardiovascular disease is the result of an unprecedented transformation in the causes of morbidity and mortality during the 20th century. Known as the *epidemiological transition,* this shift is driven by industrialization, urbanization, and associated lifestyle changes, and it is taking place in every part of the world among all races, ethnic groups, and cultures. The transition is divided into four basic stages: pestilence and famine, receding pandemics, degenerative and human-made diseases, and delayed degenerative diseases. A fifth-stage, characterized by an epidemic of inactivity and obesity, may be emerging in some countries.

The *age of degenerative and human-made diseases* is distinguished by mortality from non-communicable diseases, primarily cardiovascular disease, surpassing mortality from malnutrition and infectious diseases. Caloric intake, particularly from animal fat, increases. Coronary heart disease and stroke are prevalent, and between 35 and 65% of all deaths can be traced to cardiovascular disease. Typically, the rate of death from coronary heart disease exceeds that of stroke by a ratio of 2:1-3:1. During this period, average life expectancy surpasses 50. Roughly 35% of the world's population falls into this category.

Our country appears to be in the above age.

In the *age of delayed degenerative diseases*, cardiovascular disease and cancer remain the major causes of morbidity and mortality, with cardiovascular disease accounting for 40-50% of all deaths. However, age-adjusted cardiovascular disease mortality declines, aided by preventive strategies, such as smoking cessation programs and effective blood pressure control; by acute hospital management; and by technological advances, such as the availability of bypass surgery. Coronary heart disease, stroke, and congestive heart failure are the primary forms of cardiovascular disease. About 15% of the world's population is now in the age of delayed degenerative diseases or is exiting this age and moving into the fifth stage of the epidemiologic transition.

Prevalence/Incidence of CHD (Coronary Heart Disease) in India (2)

No prospective national cohort registries of CHD in India has published CHD incidence rates. CHD prevalence rates can be estimated from several studies over the past several decades in either rural or urban cohorts. Unadjusted CHD rates have ranged from 1.6% to 7.4% in rural populations and 1% to 13.2% in urban populations. (Gupta, 2008, India Census, 2001)

In 2000, there were an estimated 29.8 million people with CHD in India, out of a total estimated population of 1.03 billion people, or a nearly 3% overall prevalence. (Gupta, 2008, India Census, 2001)

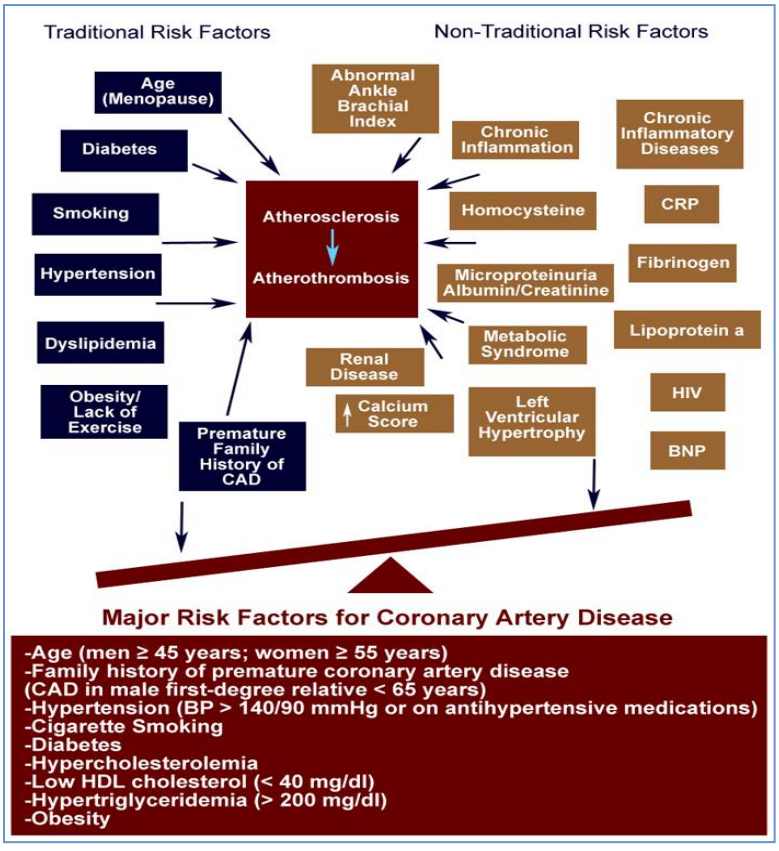
CHD affects Indians with greater frequency and at a younger age than counterparts in developed countries, as well as many other developing countries. Age-standardized CVD death rates in people 30-69 years old are 180 per 100,000 in Britain, 280 per 100,000 in China, and 405 per 100,000 in India. Also, 50% of CHD-related deaths in India occur in people <70 years of age,

whereas only 22% of CHD-related deaths in Western countries occur in this age group. (Gaziano, 2006)

Pathogenesis of Coronary Artery Disease (3)

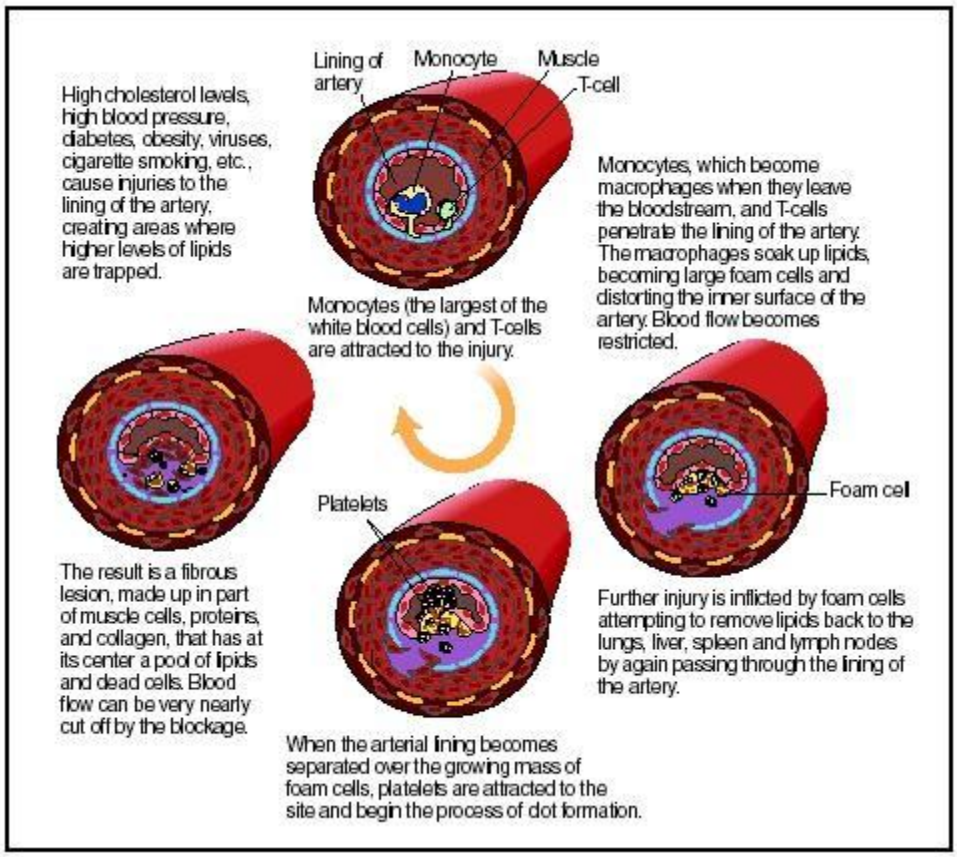
Ischemic heart disease remains the most common cardiac condition encountered by cardiac anaesthesiologists. Despite tremendous advances in our understanding of primary and secondary preventive measures and associated changes in age-adjusted mortality, it is almost certain that ischemic heart disease will retain its primary position as an indication for surgical interventions such as revascularization procedures and surgical management of heart failure. The risk factors for coronary artery disease are depicted in the figure below.

Figure 1. Major Risk Factors for Coronary Artery Disease



Atherosclerotic disease is initiated by the response of the wall (specifically, the endothelium) to injury. Injury to the endothelium can be induced by abnormal flow patterns (e.g., shear stress at points of bifurcation) and is exacerbated by well-established risk factors for coronary artery disease, including hypertension, hyperlipidemia, diabetes, smoking, and likely infections. The molecular mechanisms involved are complex. Importantly, it is now well established that oxidant signaling under physiologic circumstances, as well as oxidant stress and imbalance between production of reactive oxygen species and endogenous scavenging mechanisms in pathophysiologic circumstances, are pivotal factors in the development of atherosclerosis in the vasculature.

Figure 2. Development of an atherosclerotic plaque



Progression of atherosclerosis has been characterized into various phases, as has its correlation with clinical syndromes, including the relationship between plaque stability and acute coronary syndromes (ACS). These syndromes occur when atherosclerotic plaques rupture or fissure because of degradation of their fibrous caps by enzymes such as metalloproteinases. The release of multiple mediators, including thromboxane, serotonin, and adenosine biphosphate, causes vasoconstriction, platelet aggregation, thrombus formation, and fibrous proliferation, the fundamental mechanisms underlying the development of ACSs.

The clinical features of ischemic heart disease are not only angina, myocardial infarction, ischemic cardiomyopathy, and sudden death. They also include phenomena of stunning, hibernation, and ischemic preconditioning.

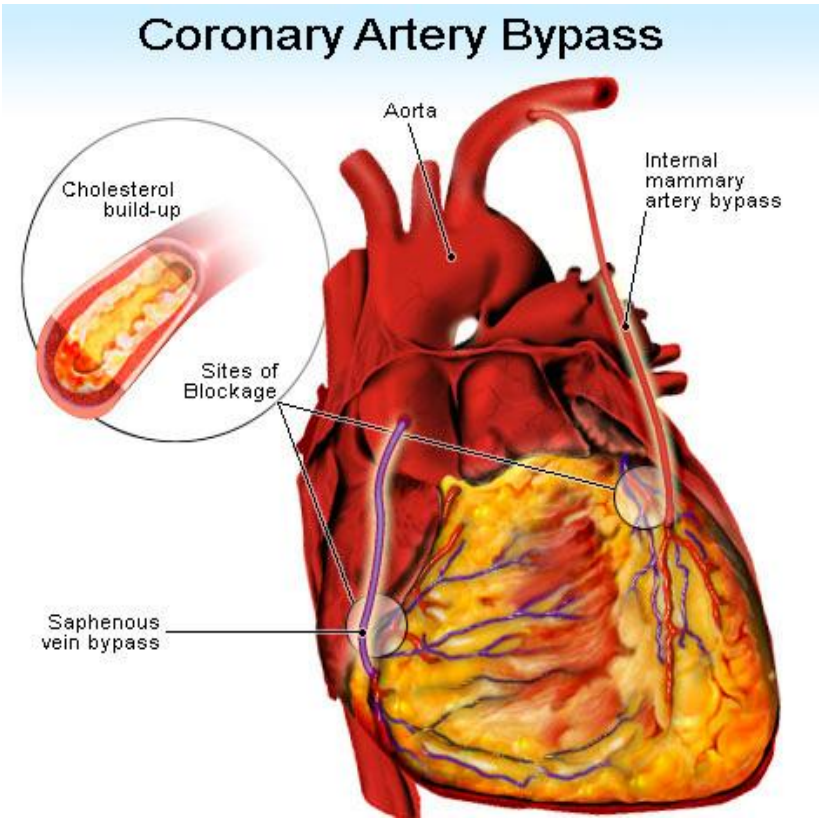
Coronary Artery Bypass Graft Surgery (CABG) (4)

CABG aims to revascularize coronary arteries, with a flow-reducing luminal stenosis, supplying a viable and sizeable area at risk. The most frequently grafted coronary arteries are the epicardial vessels, but intramural grafting is part of routine coronary surgery.

The initial development of CABG was made possible with the use of extracorporeal circulation and induced ventricular fibrillation. When aortic cross-clamping is used to perform the distal anastomoses, the myocardium can be protected against ensuing ischaemia by several methods.

CABG is performed using extracorporeal circulation (CPB) in 70% of all operations worldwide. This includes a median sternotomy, Internal thoracic artery(s) dissection, and, when appropriate, simultaneous harvesting of the venous and or radial artery grafts. CPB requires profound anticoagulation using heparin for an activated clotting time of >400 s. Partial or total aortic cross-clamping allows the construction of proximal anastomoses. A single cross-clamp may be preferred with the aim of reducing athero-embolic events.

Figure 3. Coronary Artery Bypass Graft Surgery



Indications for elective CABG (5)

a. CABG to improve survival

1. CABG to improve survival is recommended for patients with significant (>50% diameter stenosis) left main coronary artery stenosis
2. CABG to improve survival is beneficial in patients with significant (>70% diameter) stenoses in 3 major coronary arteries (with or without involvement of the proximal LAD artery) or in the proximal LAD plus 1 other major coronary artery
3. CABG to improve survival is beneficial in survivors of sudden cardiac death with presumed ischemia-mediated ventricular tachycardia caused by significant (>70% diameter) stenosis in a major coronary artery

4. CABG to improve survival is reasonable in patients with significant (>70% diameter) stenoses in 2 major coronary arteries with severe or extensive myocardial ischemia (eg, high-risk criteria on stress testing, abnormal intracoronary hemodynamic evaluation, or >20% perfusion defect by myocardial perfusion stress imaging) or target vessels supplying a large area of viable myocardium
5. CABG to improve survival is reasonable in patients with mild-moderate LV systolic dysfunction (EF 35% to 50%) and significant (>70% diameter stenosis) multivessel CAD or proximal LAD coronary artery stenosis, when viable myocardium is present in the region of intended revascularization

b. CABG to improve symptoms

1. CABG to improve symptoms is beneficial in patients with 1 or more significant (>70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite goal directed medical therapy
2. CABG to improve symptoms is reasonable in patients with 1 or more significant (>70% diameter) coronary artery stenoses and unacceptable angina for whom goal directed medical therapy cannot be implemented because of medication contraindications, adverse effects, or patient preferences

Early clinical outcome at 3 months after CABG is characterized by a 1–2% mortality rate and a 1–2% morbidity rate for each of the following events: stroke, renal, pulmonary and cardiac failure, bleeding, and wound infection. The early risk interval in CABG extends for 3 months, is multi-factorial, and depends on the interface between technical variability and patient comorbidity (4).

Anaesthesia for patients coming for elective CABG

Optimal anesthesia care in CABG patients (5) should include

1) A careful preoperative evaluation and treatment of modifiable risk factors

2) Proper handling of all medications given preoperatively

3) Establishment of central venous access and careful cardiovascular monitoring

4) Induction of a state of unconsciousness, analgesia, and immobility

5) A smooth transition to the early postoperative period, with a goal of early extubation, patient mobilization, and hospital discharge.

Attention should be directed at preventing or minimizing adverse hemodynamic and hormonal alterations that may induce myocardial ischemia or exert a deleterious effect on myocardial metabolism (as may occur during induction, intubation, surgical stimulation and cardiopulmonary bypass [CPB])

Relevant Cardiac physiology (6)

Prevention or treatment of ischemia during coronary artery bypass graft (CABG) surgery reduces the incidence of perioperative myocardial infarction. Hemodynamic management is tailored to avoid factors known to increase myocardial oxygen demand ($M\dot{V}O_2$), particularly during the vulnerable pre-CPB period. Optimizing oxygen delivery to the myocardium is equally important for the successful management of these patients because it is well recognized that most ischemic events occur with minimal or no change in $M\dot{V}O_2$

Myocardial Oxygen Demand

The principal determinants of $M\dot{V}O_2$ are wall tension and contractility. Laplace law states that wall tension is directly proportional to intra-cavitary pressure and ventricular radius, and

inversely proportional to wall thickness. Therefore, myocardial oxygen demand can be reduced by interventions that (1) prevent or promptly treat ventricular distention, and (2) decrease intra-ventricular pressure.

Myocardial Oxygen Supply

Increases in myocardial oxygen requirements can be met only by raising coronary blood flow. Blood oxygen content is important, as is oxygen extraction by the myocardium, but these are infrequent reasons for intra-operative ischemia because oxygenation and blood volume are usually well maintained during anesthesia. Blood in the coronary sinus is 50% saturated (Po_2 approximately 27 mm Hg), and although extraction can be increased somewhat under conditions of stress, it is inadequate to meet the continuously increasing demand. Therefore, the principal mechanism for matching oxygen supply to alterations in $M\dot{V}O_2$ is exquisite regulation and control of coronary blood flow.

Coronary Blood Flow

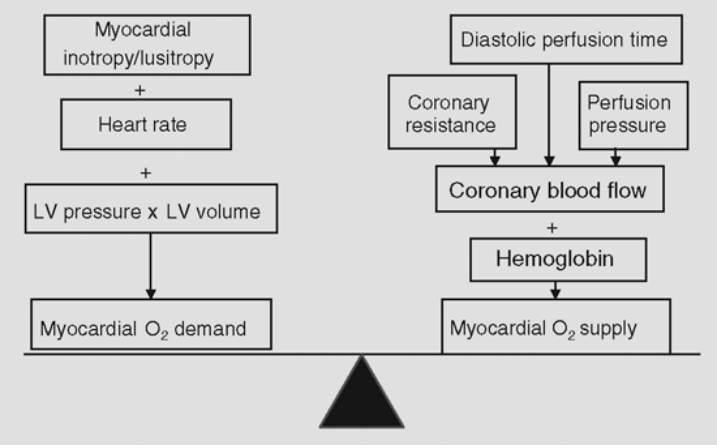
The critical factors that modify coronary blood flow are the perfusion pressure and vascular tone of the coronary circulation, the time available for perfusion (determined by heart rate), the severity of intra-luminal obstructions, and the presence of (any) collateral circulation. The area most vulnerable to ischemia is the subendocardium of the left ventricle (LV), where metabolic requirements are increased because of greater systolic shortening.

Perfusion of the LV subendocardium takes place almost entirely during diastole, whereas the right ventricular subendocardium is perfused mostly during systole, assuming pulmonary hypertension is not present. This temporal disparity is explained by the different intra-ventricular pressures developing during systole.

The LV coronary perfusion pressure is often defined as the difference between aortic diastolic pressure and left ventricular end-diastolic pressure. In the presence of intra-luminal obstruction or increased vascular tone, this pressure gradient is reduced. Therefore, a low left ventricular end-diastolic pressure is ideal both in terms of improving perfusion (higher pressure gradient) and of reducing $M\dot{V}O_2$ (decreased ventricular volume and wall tension). The consequences of systemic pressure are more difficult to predict; for example, increasing perfusion pressure may increase $M\dot{V}O_2$. However, it has been shown clinically that tachycardia is the most important trigger of intra-operative and peri-operative ischemia.

Alterations in the tone of the small intra-myocardial arterioles regulate diastolic vascular resistance, allowing the matching of oxygen supply with metabolic demand over a wide range of perfusion pressures. The difference between auto regulated, baseline flow, and blood flow available under conditions of maximal vasodilation is termed coronary vascular reserve, and is normally 3 to 5 times higher than basal flow. As epicardial stenosis becomes more pronounced, progressive vasodilation of these resistance vessels allows preservation of basal flow, but at the cost of reduced reserve. Whenever demand increases above available reserve, signs, symptoms, and metabolic evidence of ischemia develop.

Figure 4. Myocardial Oxygen Demand-Supply balance



Role of the Anaesthesiologist in CABG (6)

Although the precise relationship between intraoperative ischemia and postoperative myocardial infarction remains controversial, there is consensus that one of the primary goals of any successful anesthetic is prevention of myocardial ischemia. Failing that, prompt identification and treatment of new ischemic episodes is essential.

Anesthetic decisions are designed to

a. Reduce and control those factors that increase myocardial oxygen demand (heart rate, contractility, and wall tension)
b. Optimize coronary blood flow, notably, maintaining coronary perfusion pressure and increasing diastolic time.

The goals for patients with coronary artery disease are "slow, small, and well perfused." Combinations of anesthetics, sedatives, muscle relaxants, and vasoactive drugs are selected to provide this hemodynamic milieu. Pharmacologic agents that may benefit coronary patients include statins and angiotensin-converting enzyme inhibitors (to stabilize the atherosclerotic plaque), and volatile anesthetics (anesthetic preconditioning).

Induction of anaesthesia (6)

The exact choice and sequence of drugs are a subtle—sometimes not so subtle—combination of art and science. The choice of specific agents (e.g., sedative, opioid, volatile drug, muscle relaxant), dose, and speed of administration depends primarily on the patient's cardiovascular reserve and desired cardiovascular profile. A smooth transition from consciousness to blissful sleep is desired without untoward airway difficulties (e.g., coughing, laryngospasm, truncal rigidity) or hemodynamic responses (e.g., hypotension from relative overdose, loss of

sympathetic tone, or myocardial depression; hypertension caused by airway insertion; or jaw thrust). A "slow cardiac induction" sometimes causes, rather than alleviates, these potential problems. However, awake tracheal intubation, after proper sedation, may be appropriate in a bull-necked, obese patient if ventilation and intubation appear to be difficult. The necessity for individual approach to each patient cannot be overemphasized.

During induction, there is a risk of hypotension due to the vasodilation caused by the inducing agent(s). Furthermore, lack of stimulation during bag and mask ventilation, prior to intubation, is also another factor. Hypotension caused during this period can cause a decrease in the myocardial oxygen supply, especially in those patients with severe stenosis of the coronary vessels, and in those with already compromised myocardium (low ejection fraction, due to previous infarct).

Various permutations and combinations have been studied to maintain the supply-demand balance. These include induction agent-opioid combinations, benzodiazepine-opioid combinations, and high dose opioid alone. Several of the newer and more short acting opioids are also being studied. Sufentenil-midazolam, ketamine-fentanyl-midazolam, propofol-fentanyl, remifentanil alone, remifentanyl-propofol, high dose alfentanil-lorazepam, alfentanil-etomidate and fentanyl- etomidate are a few (7,8,9,10,11,12,13).

Haemodynamic responses to intubation

The circulatory responses to laryngoscopy and endotracheal intubation were first documented by King *et al.* ~ in 1951(14). They found that laryngoscopy increased blood pressure and heart rate, with deep anaesthesia abolishing the response

Laryngoscopy and intubation in the lightly anaesthetized patient are accompanied by considerable increases in heart rate and arterial blood pressure. These changes are of short duration, and well tolerated by patients in the absence of cardiovascular disease. However, sudden death (vagally mediated(6)) has occurred immediately after intubation. Myocardial ischaemia, ventricular arrhythmias, left ventricular failure, and cerebral haemorrhage have all been reported with the post-intubation pressor responses.

Deep planes of anesthesia**,** brief duration of laryngoscopy, and innumerable pharmacologic regimens have been proposed for eliminating the hypertension and tachycardia associated with intubation of the trachea. None are uniformly successful, and all drug interventions carry some degree of risk, even though they may be small. Furthermore, more recent evidence suggests that intubation of the trachea is a strong stimulus for coronary vasoconstriction irrespective of the anaesthetic, because LV blood flow is dramatically altered in the absence of hemodynamic changes. Therefore, the response to tracheal intubation may be variable, although usually short-lived.

Various pharmacological regimens have therefore been tried out with varying degrees of success in blunting the intubation response without causing significant hypotension during the pre-intubation period. Theses include vasodilators, opioids, beta-blockers and calcium channel blockers (15, 18, 19, 20, 21, 23). Topical anaesthetics have also been studied and found to decrease responses during airway manipulation (16, 17).

S.K. Singhal et al have studied the haemodynamic response to McCoy blade versus Macintosh blade during laryngoscopy to find that the McCoy laryngoscope produces significantly less rise in haemodynamic parameters as compared to Macintosh laryngoscope during laryngoscopy and intubation. The forces exerted by the laryngoscope blade on the base of tongue are assumed to be

the major stimuli, which result in exaggerated response to laryngoscopy. They felt that the McCoy blade was designed in such a way as to decrease the forces exerted on the base of tongue (22, 25).

LMA insertion has also been studied to look for a decreased response when compared to intubation (24).

One of the drugs that has been studied time and again for this purpose, is Fentanyl. It has been studied in various dosages and timings to find an optimal regimen for induction and intubation in the cardiac patient (26, 27, 28, 29,33).

Fentanyl (30)

Fentanyl is a phenylpiperidine-derivative synthetic opioid agonist that is structurally related to meperidine. As an analgesic, fentanyl is 75 to 125 times more potent than morphine.

Pharmacokinetics

A single dose of fentanyl administered intravenously has a more rapid onset and shorter duration of action than morphine. The distinct time lag between the peak plasma fentanyl concentration and peak slowing on the EEG reflects the effect-site equilibration time between blood and the brain for fentanyl, which is 6.4 minutes. The grater potency and more rapid onset of action reflect its greater lipid solubility, which facilitates its passage across the blood-brain barrier. Its rapid distribution to inactive tissues leading to an associated increase in plasma concentration reflects the short duration of action of a single dose of fentanyl.

When multiple intravenous doses of Fentanyl are administered are administered or when there is continuous infusion of the drug progressive saturation of these inactive tissues sites occurs. As a result, the plasma concentration of fentanyl does not decrease rapidly, and the duration of

analgesia, as well as the depression of ventilation, may be prolonged. Cardiopulmonary bypass causes clinically insignificant effects on the pharmacokinetics of fentanyl.

Metabolism

Fentanyl is extensively metabolized by N-demethylation, producing norfentanyl, hydroxypropionyl-fentanyl, and hydroxypropionyl-norfentanyl. Norfentanyl is structurally similar to normeperidine and is the principal metabolite of fentanyl in humans. It is excreted by the kidneys and can be detected in the urine for 72hours after a single IV dose of fentanyl. The pharmacological activity of fentanyl metabolites is believed to be minimal.

Elimination Half-Time

The elimination half-time for fentanyl is longer than morphine due to the larger volume of distribution of fentanyl though its clearance is similar to morphine. The larger volume of distribution of fentanyl is due to its greater lipid solubility and thus more rapid passage into tissues. After an intravenous bolus, more than 80% of the injected dose leaves the plasma in less than 5 minutes. The plasma concentration of fentanyl are maintained by slow reuptake from inactive tissues, which accounts for persistent drug effects that parallel the prolonged elimination half-time.

A prolonged elimination half-time for Fentanyl in elderly patients is due to decreased clearance of the opioid because volume of distribution is not changed in comparison to younger adults. This change may reflect age-related decreases in hepatic blood flow, microsomal enzyme activity, or albumin production, as fentanyl is highly bound (79-87%) to protein. For these reasons, it is likely that a given dose of Fentanyl will be effective for a longer period of time in elderly patients.

Context-Sensitive Half-Time

As the duration of continuous infusion of fentanyl increases beyond two hours, the context-sensitive half-time of this opioid becomes greater than sufentanil. This again reflects a saturation of inactive tissue sites with fentanyl during prolonged infusions and return of the opioid from peripheral compartments to the plasma. This tissue reservoir of fentanyl replaces the fentanyl eliminated by hepatic metabolism so as to slow the rate of decrease in the plasma concentration of fentanyl when the infusion is discontinued.

Cardiopulmonary Bypass

All opioids show a decrease in plasma concentration with initiation of cardiopulmonary bypass. The degree of this decrease is greater with fentanyl because a significant proportion of the drug adheres to the surface of the cardiopulmonary bypass circuit. Elimination of Fentanyl has been shown to be prolonged by cardiopulmonary bypass.

Cardiovascular effects

In comparison with morphine, fentanyl even in large doses (50µg/kg IV) does not evoke histamine release. As a result, dilation of venous capacitance vessels leading to hypotension is unlikely. Bradycardia is more prominent with fentanyl than morphine and may lead to occasional decreases in blood pressure and cardiac output. Fentanyl administration rarely causes allergic reactions.

Sevoflurane

Sevoflurane is an inhalational agent which is halogenated with fluorine. Non-pungency and rapid increases in alveolar anesthetic concentration make Sevoflurane an excellent choice for smooth and rapid inhalation inductions in pediatric and adult patients. It mildly depresses myocardial contractility. Systemic vascular resistance and arterial blood pressure decline is slightly less when compared to Isoflurane or Desflurane. Because Sevoflurane causes little, if any, rise in heart rate, cardiac output is not maintained as well as with Isoflurane or Desflurane. There is no evidence associating Sevoflurane with coronary steal syndrome. Sevoflurane may prolong the QT interval, the clinical significance of which is unknown (39).

Midazolam

Midazolam is a water-soluble benzodiazepine with an affinity for the benzodiazepine receptor, thereby facilitating GABA. Despite prompt passage across the blood-brain barrier, it has a slow effect-site equilibration time and the elimination half-time of Midazolam is 1 to 4 hours. When used for Induction, Midazolam causes a decrease in systemic vascular resistance without decreasing the cardiac output. The drop in blood pressure seen with 0.2mg/kg IV Midazolam is comparable to that seen with 3 to 4 mg/kg IV Thiopentone. Midazolam does not prevent blood pressure and heart rate responses evoked by intubation of the trachea. The effects of Midazolam on systemic blood pressure are directly related to its plasma concentration. Onset of unconsciousness is facilitated when a small dose of opioid precedes the injection of Midazolam by 1 to 3 minutes (30).

High dose fentanyl

High dose fentanyl has been studied from the late seventies, not only as an induction agent, but also for the maintenance of anaesthesia. Theodore H. Stanley et al demonstrated that large doses of fentanyl (50-100µg/kg), as the sole anaesthetic, with ventilation with oxygen, produced complete anaesthesia and minimal changes in cardiovascular dynamics in patients with coronary artery disease. They also showed that high dose fentanyl anaesthesia blocked the increases in plasma anti-diuretic hormone and cardiovascular dynamics which were so common with morphine and other anaesthetic techniques, during tracheal intubation and surgical stimulation in patients with coronary artery disease. Interestingly, they stated that fentanyl-oxygen anaesthesia was an "attractive technique" in patients with coronary artery disease (31).

In 1985 John M Murkin et al enrolled nine pre-medicated patients, chronically maintained on beta-adrenergic blocking agents and demonstrating good ventricular function without significant valvular or left main coronary artery disease, to investigate their haemodynamic responses to rapid induction of anaesthesia and tracheal intubation during elective coronary artery bypass surgery. Fentany1 50 µg/kg and Pancuronium 0.15 mg/kg were administered intravenously over 20 seconds followed by tracheal intubation 90 seconds thereafter. The rapid sequence of anaesthetic induction and tracheal intubation was well tolerated by all patients. Though statistically significant changes were detected in heart rate, pulmonary capillary wedge pressure and systemic vascular resistance, these changes were small and not considered clinically significant and no signs of ischaemia were detected on the ECG. This study demonstrated that high-dose fentanyl was capable of inducing anaesthesia rapidly, and protecting against the haemodynamic changes associated with tracheal intubation (32).

There are also studies that have shown that though high dose fentanyl was effective in maintaining stable haemodynamics in the pre-bypass period, it was not as effective during the bypass period. J. Earl Wynands et al examined whether different plasma fentanyl concentrations could maintain hemodynamic stability during coronary artery surgery. Two randomly selected groups of 10 patients were studied. Patients in group 1 received a single 75-pg/kg intravenous dose of fentanyl; patients in group 2 received the same dose but it was followed by an infusion of fentanyl at a rate of 0.75 pg/kg/min. The total dose of fentanyl in group 2 was 162 ± 6.5 pg/kg. At some point during surgery, all 10 patients in group 1

and 7 of 10 patients in group 2 had a hypertensive response. Plasma fentanyl concentrations in the two groups were not significantly different in the period 10-45 min after induction of anesthesia. At 60 min, corresponding to the time of aortic root dissection, mean plasma fentanyl concentration was statistically significantly lower in group 1 than in group 2 (13.5 ± 1.4 ng/ml and 24 ± 2.3 ng/ml, respectively, $P < 0.01$). However, no significant difference was observed in the frequency of hypertensive response between the two groups in the period before cardiopulmonary bypass. During cardiopulmonary bypass, plasma fentanyl concentrations in group 1 were 2-3 times lower than those in group 2**,** and hypertension was observed in all 10 patients in group 1 but in only 2 patients in group 2 ($P < 0.05$) (33).

As seen above, high dose fentanyl, when used alone seemed to provide commendable haemodynamic conditions during induction and intubation. Even small doses of benzodiazepine, appear to cause unacceptable hypotension (34).

High dose fentanyl, however, does pose the problem of fentanyl induced chest wall rigidity, which can impair adequate ventilation with bag and mask and cause haemodynamic disturbances (35). This may be circumvented by giving a priming dose of Vecuronium after an initial bolus of

fentanyl. However adequate blockade with a neuromuscular blocking agent does provide excellent conditions for intubation, in patients induced with high dose fentanyl.

Fentanyl at doses above 50µg/kg has been known to increase the vasopressor requirement post operatively (36). There have also been concerns about high dose fentanyl decreasing circulating catecholamines leading to myocardial depression (37). Delayed respiratory depression (38) also is an argument against high dose fentanyl, but does not take on much significance in centers where post CABG patients are electively ventilated overnight, in the intensive care unit.

Justification

Though high dose fentanyl seems to have gone out of vogue over the past two decades for various reasons, this study attempts to show that Fentanyl provides far superior haemodynamics during induction and intubation. It is compared to the commonly used combination induction technique (Low dose Fentanyl, midazolam and Sevoflurane) which is currently in practice in many centers including ours. A major limiting factor to the use of the more recently available short acting opioids in our set-up, is the cost.

Research question

In patients coming for elective myocardial revascularization surgery, does High dose Fentanyl provide greater haemodynamic stability during induction and intubation than the Multiagent combination technique (Low dose Fentanyl-Midazolam-Sevoflurane)?

METHODOLOGY

Brief summary of the study

This study was a prospective, randomized, controlled trial comparing the effects of two Induction techniques- High dose Fentanyl and Multiagent Combination induction with regard to haemodynamic stability in the induction phase of anaesthesia in patients undergoing Coronary Revascularisation Surgery.

Our hypothesis was that High dose Fentanyl causes greater Haemodynamic stability during this period, when compared to the combination technique. Haemodynamic stability is important in Cardiac patients during induction of anaesthesia, as heart rates and blood pressures that are either too low or too high can stress the already compromised heart and cause further myocardial ischemia and decompensation.

The research proposal was discussed by the Research and Ethics Committees on and clearance was obtained.

The study was conducted on 70 adults (40 – 75 years, ASA II-III) undergoing elective coronary revascularization surgery, with 35 patients in each arm. Written informed consent was obtained from all patients enrolled in the study, on the pre-operative day. The following were documented – demographic data, ASA grade, ECG and ECHO findings, and current medications.

Each patient entering the study was assigned a study number and was randomized into either group. Therefore, at the end of the study, there were 35 patients in the high dose Fentanyl group, and 35 patients in the Multi-agent group. The induction technique to be used was decided as per randomization and intimated to the concerned anaesthesiologist on the day before surgery.

All the patients enrolled in the study were given routine pre-anaesthetic orders. All preoperative cardiac medications except ACE inhibitors were continued on the morning of surgery. Oral pre-medication with Lorazepam 2mg was administered on the night before surgery and one and a half hours prior to induction. Patients more than 60 years of age were given only 1mg Lorazepam, instead of 2mg.

Once the patient was on table, Pulse oximeter and Electrocardiogram leads were applied. A large bore peripheral intravenous access and Radial arterial line were placed before induction.

The patient monitors used during the study were: Pulse oximetry, Electrocardiography (leads II and V), Invasive Radial Arterial blood pressure monitoring and Capnography.

The patient's hemodynamic and physiological parameters were recorded in a data sheet which was provided to the concerned anaesthesiologist. Baseline readings of pulse, blood pressure (systolic, diastolic and mean) and oxygen saturation were taken prior to induction. The patient was then induced with the allotted technique over 6 minutes. Drugs were given over 2 minutes, and the patient was hand ventilated with bag and mask over 4 minutes. Pulse, blood pressure and oxygen saturation were recorded at every minute during induction and mask ventilation. So there were 6 sets of readings prior to intubation. The last reading was taken 1minute after tracheal intubation.

During this time hypotension was treated depending on the heart rate. Hypotension was treated if the systolic blood pressure was less than 90mmHg or if the mean blood pressure was less than 60mmHg. For hypotension with a heart rate below and above 60 beats/minute, Ephedrine and

Phenylephrine were used, respectively. Bradycardia was treated only if there was accompanying hypotension. The number of vasopressor boluses used were documented.

Dosages of each anaesthetic agent used were also documented. Presence of chest wall rigidity was also noted. The study ended here.

Methodology in detail

Intervention and Comparator agent

Intravenous induction agent(s):

High dose Fentanyl: 50 micrograms per kg body weight. A small priming dose of Vecuronium (0.2mg) was administered after the first 100µ of fentanyl to prevent chest wall rigidity.

Multi-agent Combination Technique: 5 micrograms per kg body weight, Midazolam (0.05mg per kg body weight) and Sevoflurane(2 to 6 %)

Study design

A participant-blinded Randomized Controlled Trial

Study setting and population

This study was conducted on patients who were admitted for elective Coronary Artery Bypass Graft Surgery with the permission of the Department of Cardio Thoracic Surgery.

Key Criteria

a. Inclusion Criteria:

1. Patients who need Coronary artery surgery
2. Age: 40 to 75 years
3. ASA grade II to III
4. Ejection fraction more than 40%

b. Exclusion Criteria:

1. Previous Cardiac Surgery
2. Renal or Hepatic Dysfunction (Elevated Serum SGOT/ SGPT/ Creatinine)
3. Hemodynamic instability requiring medical or mechanical support
4. Active congestive cardiac failure
5. Severe chronic obstructive pulmonary disease as shown by FEV1 less than 50%.

Method of randomization:

The method of randomization was block-randomization, given the sample size was small (to ensure equal number of patients in each limb). A randomization list was generated by the block randomization method with varying sizes of blocks using STATA 10 (StataCorp, College Station, TX, USA). The other advantage of using this program was that if the study had to be stopped before the entire sample size was achieved, there would still be almost equal numbers in each group.

Method of allocation concealment:

Each patient was assigned a study number after they had completed the consent process. Participants were then allocated to one of the two study groups depending on the induction technique written against their study number in the computer generated randomization list.

Blinding and masking:

This study was participant blinded. The patient was unaware of what induction agent was going to be administered to him/her.

Primary Outcome:

Presence or absence of Haemodynamic Instability:

1. Drop in Systolic Blood Pressure less than 90mmHg or Mean Blood Pressure less than 60 mm Hg
2. Increase in Systolic Blood Pressure more than 130mmHg after intubation
3. Drop in Heart Rate to less than 60 beats/minute accompanied by hypotension
4. Increase in Heart Rate to more than 20% of the baseline
5. Requirement of vasopressors till intubation were measured by whether or not Ephedrine(5mg) or Phenylephrine(50/100mic) boluses were administered

Secondary Outcomes:

1. Incidence of chest wall rigidity was a subjective measurement
2. Drop in Oxygen saturation due to difficulty in mask ventilation

Target sample size and rationale:

The sample size was calculated based on the following assumptions

Incidence of the hemodynamic instability in the low dose fentanyl = 35%

Incidence of the hemodynamic instability in the high dose fentanyl = 5%

Effect size = 30%

Power = 80%

Significance level = 5%

To find a 30% difference in the primary outcome between the two groups, with 80% power and 5% level of significance, the sample size was calculated as 35 in each group (70 total sample size).

Phase of trial:

Phase III

Duration of trial:

1 year and 9 months

Protocol variations: Rules for

a. Interim analyses: Nil
b. For withdrawal of participants: If a patient refuses to give consent or if a patient acutely worsens after consent, such a participant will not be randomized and will be withdrawn from the study
c. For premature stopping of trial: Nil

   A Data monitoring committee was not appointed

Post Trial benefits and care:

Routine post operative care which is given for all patients who have undergone coronary vascular bypass graft surgery was given for all patients who had participated in the study. Following immediate post-operative care in the Cardio-thoracic ICU, they were cared for in the wards till discharge. The PI and co-investigators were accessible and available for any post-trial care.

Statistical Analyses:

a. Statistical methods to be used for the primary outcome: Included description of methods to estimate the strength of the effect (e.g.: Odds ratios, relative risks, etc)
b. Baseline comparisons were done. The primary outcome (incidence of hemodynamic instability) was compared between the two study groups using two-sample proportion test.
c. Outcomes like administration of vasopressor boluses and incidence of chest wall rigidity were compared between the two groups either using independent two-sample t-test or proportion test, as appropriate.

Measurements

Primary Outcome Measure: Presence of Haemodynamic instability

a. ***Mean heart rate and blood pressure:*** A comparison between the mean heart rates and blood pressures during the period of induction and post intubation in the intervention and control groups.

- Heart rate: Baseline, every minute for 6 minutes of induction and 1 minute post-intubation.
- Blood pressure (Systolic, Diastolic and mean): Baseline, every minute for 6 minutes of induction and 30 seconds post-intubation.

b. ***Vasopressor requirement:*** Number of subjects requiring vasopressor boluses (Ephedrine or Phenylephrine) in each group.

Secondary Outcome Measure: Presence of chest wall rigidity

a. ***Difficulty in bag and mask ventilation:*** Subjective measure of ease of bag and mask ventilation prior to intubation

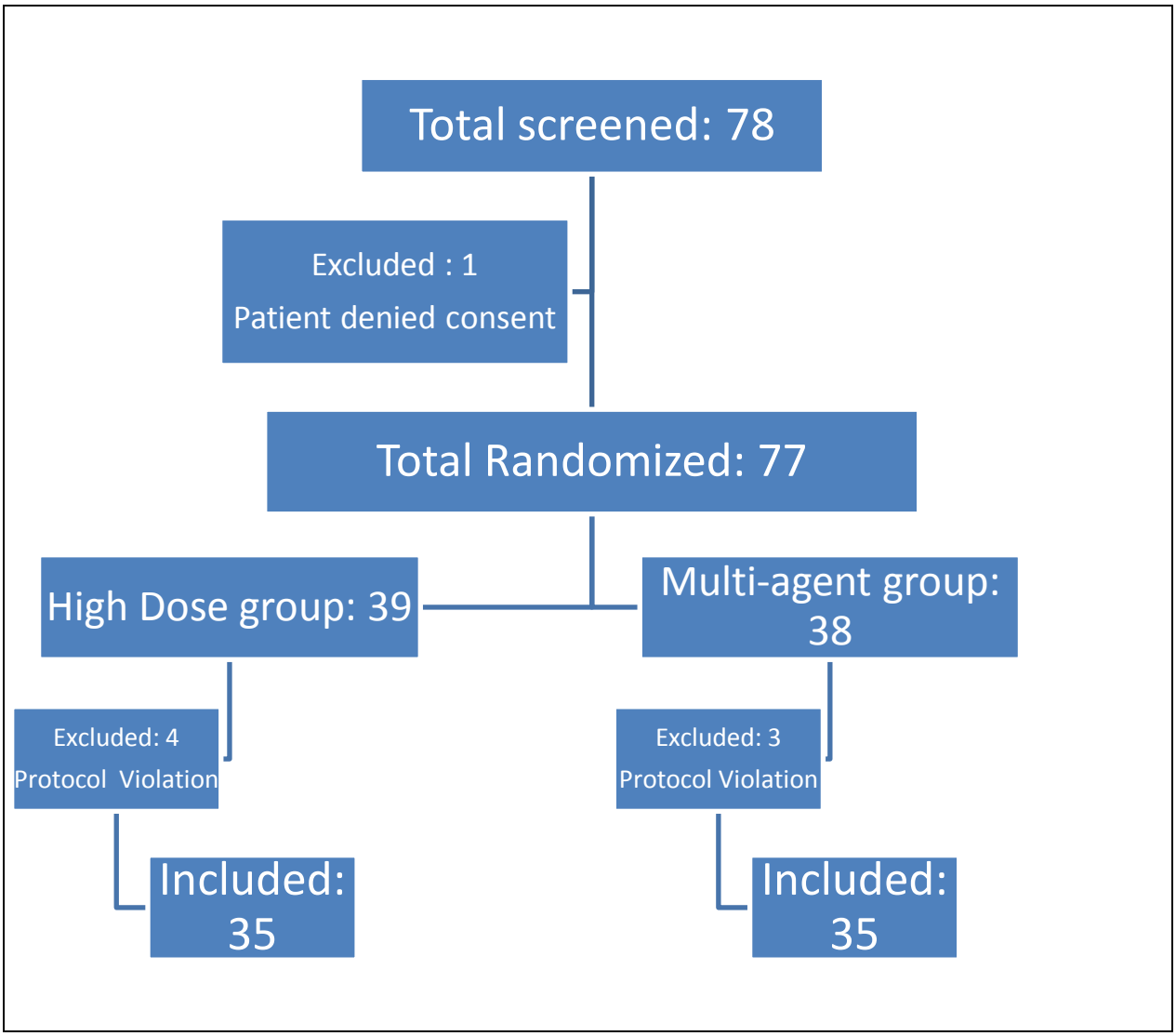
b. ***Drop in oxygen saturation:*** Oxygen saturation monitoring to see if there is a significant drop in saturation.

The Data sheet used for the study is found in Appendix 1.

RESULTS

A total of 78 patients were screened for the study. They were randomized using a randomization code generated by STRATA 10. 7 patients were excluded due to protocol violation, while 1 patient was excluded for declining participation in the study. So finally, a total of 35 patients were included in the high dose Fentanyl group (group H) and 35 in the multi-agent combination technique group (group M). All the demographic data was available for all patients except one.

Figure 5. Study flow-chart



Baseline Clinical Characteristics

Table 1. Demographic characteristics

		Multi-Agent (N=35)	Percentage	High Dose (N=35)	Percentage
Age Group distribution	Up to 40 yrs	2	5.7	2	5.9
	From 41 - 50 yrs	5	14.3	4	11.8
	From 51 - 60 yrs	18	51.4	18	52.9
	From 61 - 70 yrs	7	20	8	23.5
	Above 70 years	3	8.6	2	5.9
Sex distribution	Male	31	88.6	31	88.6
	Female	4	11.4	4	11.4

Table 1 above, shows that there were 31 males and 4 females in each group. The age distribution also shows that there is a comparable distribution of age in both the Multi-agent and High dose groups.

Table 2. Pre operative Status

	Multi-Agent (N=35)	Percentage	High Dose (N=35)	Percentage
Abnormal ECG	16	45.7	30	85.7
Ejection fraction				
31 - 40 %	0	0	1	2.9
41 - 50 %	3	8.6	15	42.9
51 - 60 %	32	91.4	19	54.3
Diabetes mellitus	11	31.4	15	42.9
Hypertension	18	51.4	19	54.3
COPD	0	0	2	5.7
CKD	3	8.6	1	2.9
PTCA	3	8.6	3	8.6

Table 2 above shows the pre operative disease conditions in the subjects. 85.7% of the patients in the High dose group had abnormal ECGs when compared to 45.7% in the Multi-agent group. 91.4% of the patients in the Multi-agent group had a normal Ejection Fraction, when compared to 54.3% in the High dose group. The pre operative co-morbid diseases (Diabetes Mellitus, Hypertension, COPD and Chronic Kidney Disease) were more or less evenly distributed among both groups. 3 patients form both groups were status post percutaneous trans-coronary angioplasty.

Table 3. Pre operative Medications

	Multi-Agent (N=35)	Percentage	High Dose (N=35)	Percentage	p-value
Blocker	30	85.7	32	91.4	0.71
ACE Inhibitor	15	42.9	24	68.6	0.05
AR Blocker	2	5.7	2	5.7	1
CC Blocker	6	17.1	1	2.9	0.1
Nitrates	29	82.9	24	68.6	0.26
Digoxin	0	0	1	2.9	1
Diuretic	4	36.4	7	20	0.51
Anti-Anginal drug	24	68.6	24	68.6	1

Table 3 above shows that at the baseline, the use of β blocker, Angiotensin receptor blocker, Calcium channel blocker, Nitrates, digoxin, diuretic and anti-anginal drugs was similar in both the Multi-agent and High dose group (p-values > 0.05). However, 24 (68.6%) patients in the High dose group while 15 (42.9%) in the low dose group were receiving ACE inhibitor. The difference in both groups was statistically significant (p-value = 0.05).

Table 4. Baseline Hemodynamic Parameters

	Multi-Agent (N=35)	Percentage	High Dose (N=35)	Percentage	p-value
Heart Rate	73.9	14.9	74.7	11.7	0.8
SBP	146.3	26.1	141.8	23.2	0.44
DBP	72.7	14.5	72.5	10.1	0.93
MAP	98.9	16.9	96.9	12.2	0.56
SpO2	99.2	1.3	99	2.2	0.69

Table 4 above shows that the heart rate, systolic, diastolic and mean blood pressures were similar at the baseline in both the Multi-agent and High dose groups (p-values > 0.05). Baseline saturation was also similar in both groups (p-value = 0.69).

Systolic Blood Pressure

Figure 6.

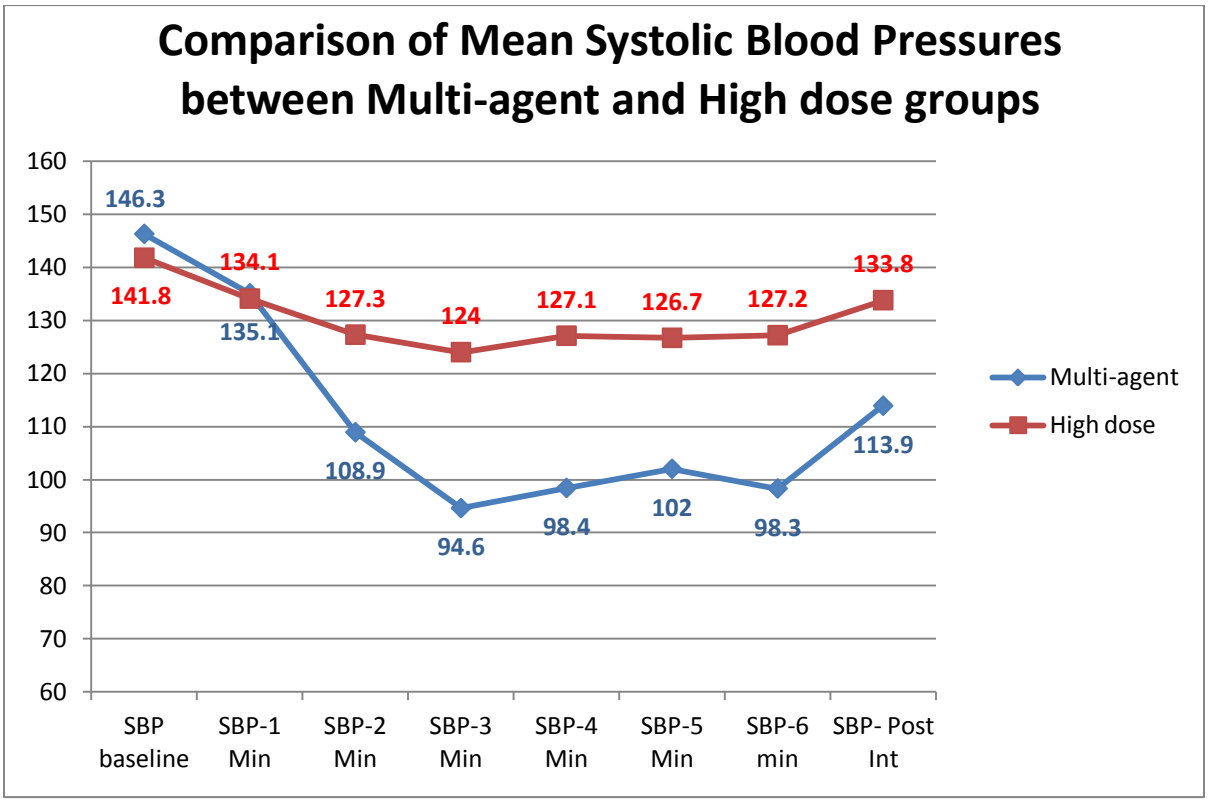


Figure 6 above, shows the mean of the systolic blood pressures at one minute intervals from the baseline, through the six minute induction period, up to 30 seconds post intubation, in the Multi-agent group and the High dose group. The baseline systolic blood pressures are comparable in both groups (146.3 and 141.8 respectively; p = 0.448; 95% CI -7.3 – 16.4). By the second minute, there is a significant fall in the systolic blood pressures of the Multi-agent group (p-value < 0.05). This difference continues till the last minute of induction, and is statistically significant.

There is also a significant difference in the systolic blood pressures, post intubation, between the Multi-agent and High dose groups (113.9 and 133.8 respectively; p <0.001; 95% CI -29.0 – -10.7).

These differences are highlighted in **Table 5**.

Comparison of Mean Systolic Blood Pressures between Multi-agent and High dose groups

Table 5.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
SBP - Baseline	Equal variances assumed	.581	.449	.764	68	.448	4.543	5.950	-7.330	16.416
	Equal variances not assumed			.764	66.859	.448	4.543	5.950	-7.334	16.419
SBP - 1 Min	Equal variances assumed	1.123	.293	.172	68	.864	1.000	5.830	-10.634	12.634
	Equal variances not assumed			.172	64.219	.864	1.000	5.830	-10.647	12.647
SBP - 2 Min	Equal variances assumed	.681	.412	-3.928	68	.000	-18.314	4.662	-27.618	-9.011
	Equal variances not assumed			-3.928	67.996	.000	-18.314	4.662	-27.618	-9.011
SBP - 3 Min	Equal variances assumed	.030	.864	-6.334	68	.000	-29.371	4.637	-38.624	-20.119
	Equal variances not assumed			-6.334	67.807	.000	-29.371	4.637	-38.625	-20.118
SBP - 4 Min	Equal variances assumed	.393	.533	-6.301	68	.000	-28.714	4.557	-37.808	-19.621
	Equal variances not assumed			-6.301	67.313	.000	-28.714	4.557	-37.810	-19.619
SBP - 5 Min	Equal variances assumed	.742	.392	-5.452	68	.000	-24.686	4.528	-33.721	-15.651
	Equal variances not assumed			-5.452	67.450	.000	-24.686	4.528	-33.722	-15.649
SBP - 6 Min	Equal variances assumed	1.502	.225	-6.657	67	.000	-28.834	4.331	-37.478	-20.189
	Equal variances not assumed			-6.638	63.807	.000	-28.834	4.343	-37.511	-20.156
SBP-Post Int	Equal variances assumed	1.243	.269	-4.377	66	.000	-19.931	4.553	-29.022	-10.839
	Equal variances not assumed			-4.348	61.284	.000	-19.931	4.583	-29.095	-10.767

Mean Arterial Blood Pressure

Figure 7.

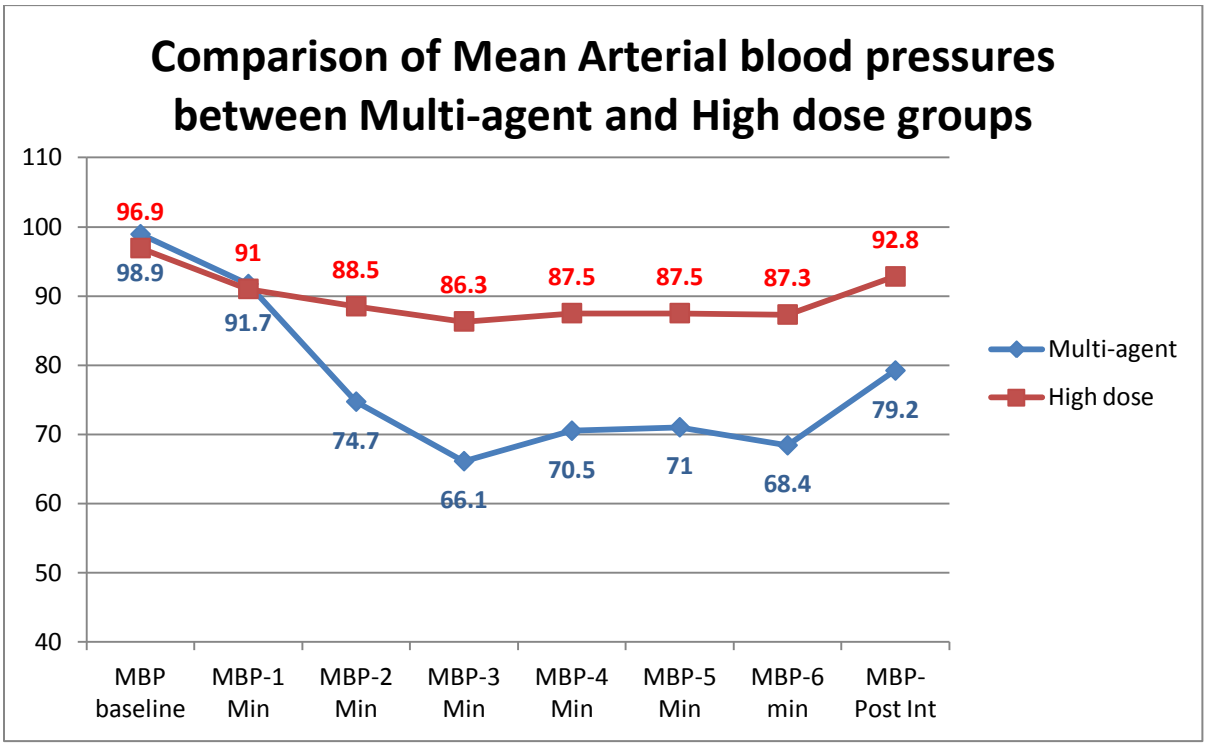


Figure 7 above, shows the mean of the Mean Arterial blood pressures (MAP) at one minute intervals from the baseline, through the six minute induction period, up to 30 seconds post intubation, in the Multi-agent group and the High dose group. The baseline mean arterial blood pressures are comparable in both groups (96.9 and 98.9 respectively; p = 0.566; 95% CI -5.0 – 9.1). By the second minute, there is a significant fall in the mean arterial blood pressures of the Multi-agent group (p- value < 0.05). This difference continues till the last minute of induction, and is statistically significant.

There is also a significant difference in the mean arterial blood pressures, post intubation, between the Multi-agent and High dose groups (79.2 and 92.8 respectively; p < 0.001; 95% CI -20.6 – -6.5). These differences are highlighted in **Table 6.**

Comparison of Mean MAP between Multi-agent and High dose groups

Table 6.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
MAP-Baseline	Equal variances assumed	2.637	.109	.576	68	.566	2.029	3.521	-4.998	9.055
	Equal variances not assumed			.576	61.960	.567	2.029	3.521	-5.011	9.068
MAP - 1 Min	Equal variances assumed	1.880	.175	.216	68	.829	.714	3.301	-5.873	7.302
	Equal variances not assumed			.216	61.774	.829	.714	3.301	-5.885	7.314
MAP - 2 Min	Equal variances assumed	.278	.600	-4.348	68	.000	-13.800	3.174	-20.134	-7.466
	Equal variances not assumed			-4.348	67.999	.000	-13.800	3.174	-20.134	-7.466
MAP - 3 Min	Equal variances assumed	.012	.914	-6.263	68	.000	-20.229	3.230	-26.673	-13.784
	Equal variances not assumed			-6.263	67.906	.000	-20.229	3.230	-26.674	-13.784
MAP - 4 Min	Equal variances assumed	1.135	.291	-5.494	68	.000	-16.914	3.078	-23.057	-10.771
	Equal variances not assumed			-5.494	66.229	.000	-16.914	3.078	-23.060	-10.768
MAP - 5 Min	Equal variances assumed	4.225	.044	-5.411	68	.000	-16.486	3.047	-22.565	-10.406
	Equal variances not assumed			-5.411	65.019	.000	-16.486	3.047	-22.570	-10.401
MAP - 6 Min	Equal variances assumed	8.463	.005	-6.505	67	.000	-18.866	2.900	-24.654	-13.077
	Equal variances not assumed			-6.456	51.922	.000	-18.866	2.922	-24.729	-13.002
MAP-Post Int	Equal variances assumed	2.546	.115	-3.872	66	.000	-13.559	3.502	-20.551	-6.567
	Equal variances not assumed			-3.843	60.307	.000	-13.559	3.528	-20.616	-6.503

Diastolic Blood Pressure

Figure 8.

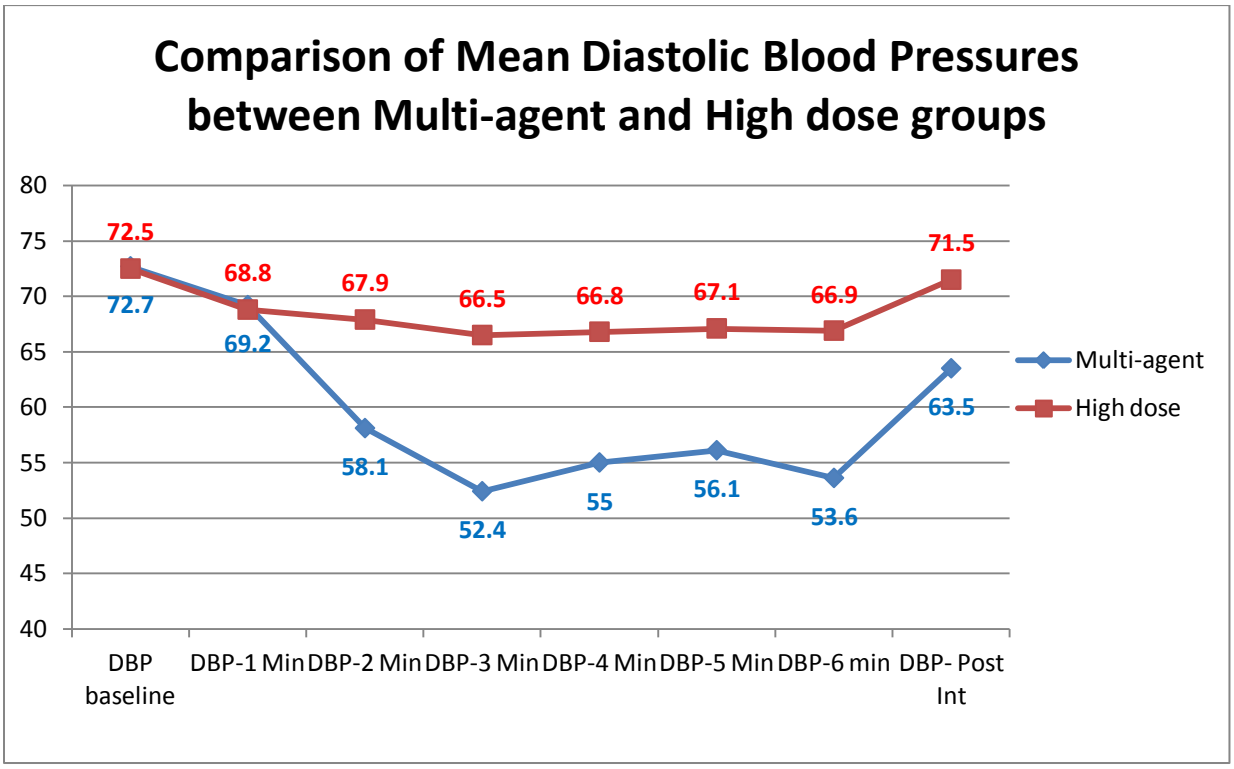


Figure 8 above, shows the mean Diastolic blood pressures (MAP) at one minute intervals from the baseline, through the six minute induction period, up to one minute post intubation, in the Multi-agent group and the High dose group. The baseline mean diastolic blood pressures are comparable in both groups (72.7 and 72.5 respectively; p = 0.939; 95% CI -5.7 – 6.2). By the second minute, there is a significant fall in the diastolic blood pressures of the Multi-agent group ($p < 0.05$). This difference continues till the last minute of induction, and is statistically significant.

There is also a significant difference in the diastolic blood pressures, post intubation, between the Multi-agent and High dose groups (63.5 and 71.5 respectively; p=0.007; 95% CI -13.7 – -2.3).

These differences are highlighted in **Table 7**.

Comparison of Mean Diastolic Blood Pressures between Multi-agent and High dose groups

Table 7.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
DBP - Baseline	Equal variances assumed	2.256	.138	.076	68	.939	.229	2.992	-5.743	6.200
	Equal variances not assumed			.076	60.589	.939	.229	2.992	-5.756	6.213
DBP - 1 Min	Equal variances assumed	2.139	.148	.151	68	.880	.371	2.458	-4.534	5.277
	Equal variances not assumed			.151	64.164	.880	.371	2.458	-4.540	5.283
DBP - 2 Min	Equal variances assumed	.715	.401	-3.681	68	.000	-9.743	2.647	-15.024	-4.461
	Equal variances not assumed			-3.681	66.215	.000	-9.743	2.647	-15.027	-4.459
DBP - 3 Min	Equal variances assumed	.001	.981	-5.094	68	.000	-14.114	2.771	-19.643	-8.586
	Equal variances not assumed			-5.094	67.949	.000	-14.114	2.771	-19.643	-8.586
DBP - 4 Min	Equal variances assumed	2.942	.091	-4.433	68	.000	-11.771	2.656	-17.071	-6.472
	Equal variances not assumed			-4.433	63.810	.000	-11.771	2.656	-17.077	-6.466
DBP - 5 Min	Equal variances assumed	7.026	.010	-4.429	68	.000	-11.029	2.490	-15.997	-6.060
	Equal variances not assumed			-4.429	62.012	.000	-11.029	2.490	-16.006	-6.051
DBP - 6 Min	Equal variances assumed	13.522	.000	-5.517	67	.000	-13.282	2.408	-18.088	-8.477
	Equal variances not assumed			-5.471	49.675	.000	-13.282	2.428	-18.159	-8.405
DBP-Post Int	Equal variances assumed	2.818	.098	-2.796	66	.007	-8.001	2.861	-13.713	-2.288
	Equal variances not assumed			-2.768	57.045	.008	-8.001	2.890	-13.789	-2.213

Heart Rate

Figure 9.

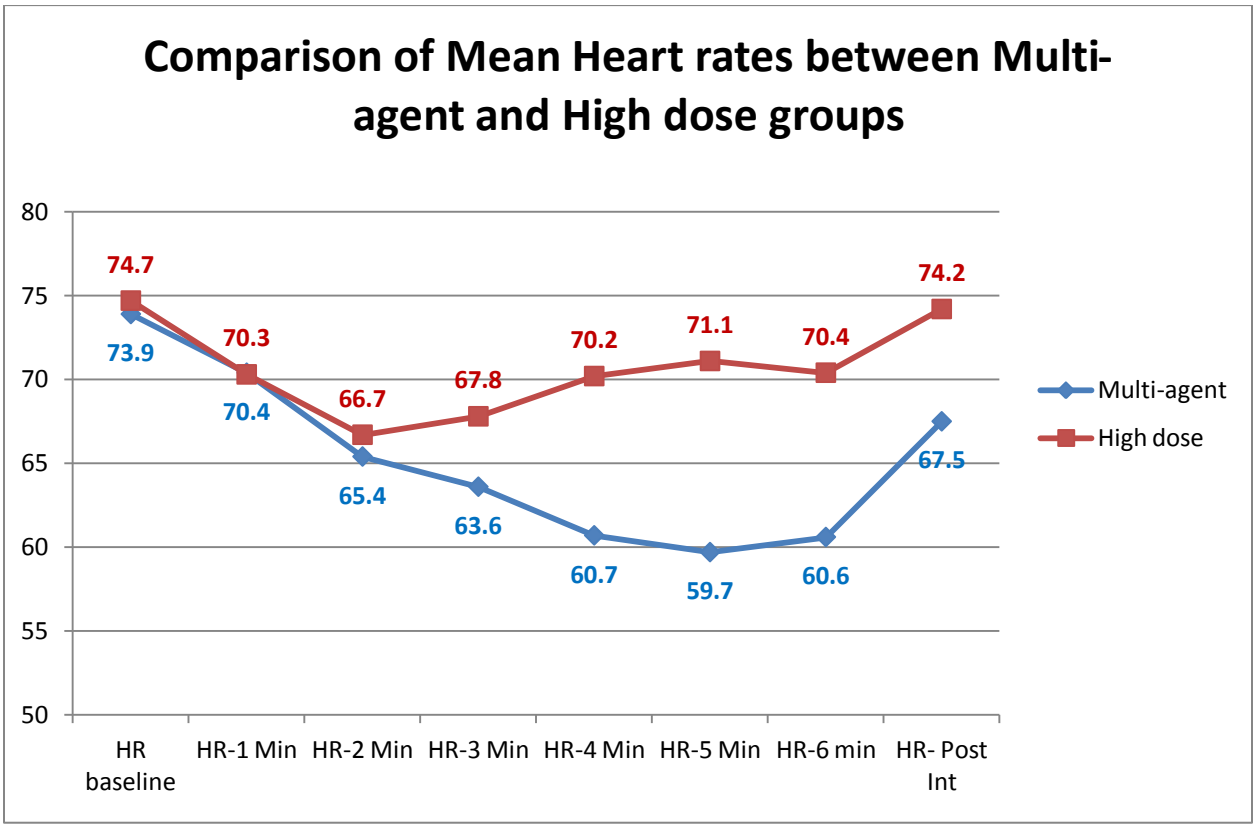


Figure 9 above shows the mean of the heart rates at one minute intervals from the baseline, through the six minute induction period, up to one minute post intubation, in the Multi-agent group and the High dose group. The baseline heart rates are comparable in both groups (73.9 and 74.7 respectively; p=0.804, CI 95% -7.2 – 5.6). By the fourth minute of induction, the heart rates in the Multi-agent group are significantly lower than those of the High dose group (p values < 0.05).

There is also a significant difference in the post intubation post-intubation readings. The heart rate is lower in Multi-agent group (67.5 and74.2; p = 0.0; 95% CI -12.6 – -0.7).

These differences are highlighted in **Table 8.**

Comparison of Mean Heart Rates between Multi-agent and High dose groups

Table 8.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
HR-Baseline	Equal variances assumed	3.213	.078	-.250	68	.804	-.800	3.203	-7.191	5.591
	Equal variances not assumed			-.250	64.396	.804	-.800	3.203	-7.197	5.597
HR- 1 Min	Equal variances assumed	.258	.613	.035	68	.972	.114	3.267	-6.405	6.634
	Equal variances not assumed			.035	66.983	.972	.114	3.267	-6.407	6.636
HR - 2 Min	Equal variances assumed	.089	.767	-.445	68	.657	-1.229	2.758	-6.732	4.275
	Equal variances not assumed			-.445	67.881	.657	-1.229	2.758	-6.732	4.275
HR - 3 Min	Equal variances assumed	.330	.567	-1.544	68	.127	-4.171	2.702	-9.563	1.221
	Equal variances not assumed			-1.544	67.817	.127	-4.171	2.702	-9.564	1.221
HR - 4 Min	Equal variances assumed	.107	.744	-3.211	68	.002	-9.429	2.936	-15.287	-3.570
	Equal variances not assumed			-3.211	67.987	.002	-9.429	2.936	-15.287	-3.570
HR - 5 Min	Equal variances assumed	.485	.489	-4.155	68	.000	-11.400	2.744	-16.875	-5.925
	Equal variances not assumed			-4.155	67.839	.000	-11.400	2.744	-16.875	-5.925
HR - 6 Min	Equal variances assumed	.039	.844	-3.659	67	.000	-9.753	2.665	-15.073	-4.433
	Equal variances not assumed			-3.659	66.880	.001	-9.753	2.666	-15.074	-4.432
HR-Post Int	Equal variances assumed	1.008	.319	-2.223	66	.030	-6.669	3.000	-12.660	-.679
	Equal variances not assumed			-2.226	65.998	.029	-6.669	2.996	-12.650	-.688

Ephedrine Administration

Comparison of Ephedrine Bolus Administration between Multi-agent and High dose groups

Table 10.

	Multi-agent group (N=35)	Percentage	High Dose group (N= 35)	Percentage
Ephedrine bolus administered	**7**	**20%**	**0**	**0%**
Ephedrine not administered	**28**	**80%**	**35**	**100%**

Table 11.

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	7.778[a]	1	.005		
Continuity Correction[b]	5.714	1	.017		
Likelihood Ratio	10.483	1	.001		
Fisher's Exact Test				.011	.006
Linear-by-Linear Association	7.667	1	.006		
N of Valid Cases[b]	70				

As shown in **Table 10** above**, 7** patients in the Multi-agent group received Ephedrine boluses, whereas **none** of the patients in the High dose group received Ephedrine. The difference is shown to be statistically significant in **Table 11** using the Chi-square test (p- value= 0.006).

Phenylephrine Administration

Comparison of Phenylephrine Bolus Administration between Multi-agent and High dose groups

Table 12.

	Multi-agent group (N=35)	Percentage	High Dose group (N= 35)	Percentage
Phenylephrine bolus administered	**29**	**82.9%**	**1**	**2.9%**
Phenylephrine not administered	**6**	**17.1%**	**34**	**97.1%**

Table 13.

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	45.733[a]	1	.000		
Continuity Correction[b]	42.525	1	.000		
Likelihood Ratio	54.455	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	45.080	1	.000		
N of Valid Cases[b]	70				

As shown in **Table 13** above, **29** patients in the Multi-agent group received Phenylephrine boluses, whereas only **1** patient in the High dose group received Phenylephrine. The difference is shown to be statistically significant in Table – using the Chi-square test (p-value < 0.001).

Chest wall Rigidity

Comparison of the Incidence of Chest wall Rigidity between Multi-agent and High dose groups

Table 14.

	Multi-agent group (N=35)	Percentage	High Dose group (N= 35)	Percentage
Chest wall Rigidity present	**0**	**0%**	**2**	**5.7%**
Chest wall Rigidity absent	**35**	**100%**	**33**	**94.3%**

Table 15.

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.059[a]	1	.151		
Continuity Correction[b]	.515	1	.473		
Likelihood Ratio	2.831	1	.092		
Fisher's Exact Test				.493	.246
Linear-by-Linear Association	2.029	1	.154		
N of Valid Cases[b]	70				

Table 14 above shows that chest wall rigidity was seen in **2** patients in the high dose group, while there were **no patients** with chest wall rigidity in the Multi-agent group. However, **Table 25** goes on to show that this difference is not statistically significant (p- value = 0.246).

Oxygen Saturation

Figure 10.

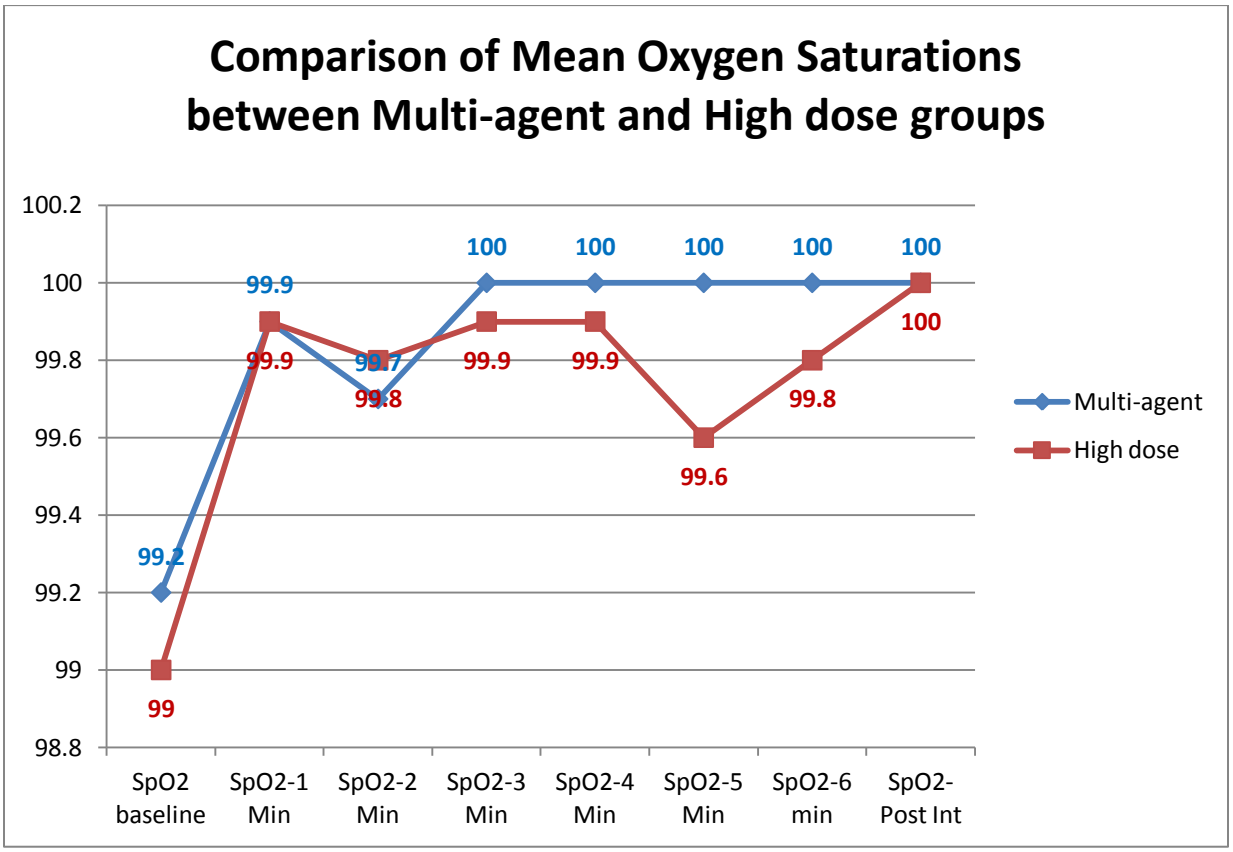


Figure 10 above, shows the mean Oxygen saturations at one minute intervals from the baseline, through the six minute induction period, up to 30 seconds post intubation, in the Multi-agent group and the High dose group. The baseline mean Oxygen saturations are comparable in both groups (99.2 and 99.0 respectively; p = 0.693; 95% CI -0.7 – 1.0). Though the values on the High dose group-curve appear lower than those on the Multi-agent group-curve, the difference was not statistically significant. This is shown in **Table 16.**

Comparison of Oxygen Saturation between the High dose and Multi-agent groups

Table 16.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
SPO2-Baseline	Equal variances assumed	1.086	.301	.396	68	.693	.171	.433	-.692	1.035
	Equal variances not assumed			.396	55.652	.694	.171	.433	-.696	1.039
SpO2 - 1 Min	Equal variances assumed	.002	.962	.000	68	1.000	.000	.185	-.368	.368
	Equal variances not assumed			.000	65.455	1.000	.000	.185	-.369	.369
SPO2 - 2 Min	Equal variances assumed	3.917	.052	-1.012	68	.315	-8.686	8.585	-25.816	8.445
	Equal variances not assumed			-1.012	34.078	.319	-8.686	8.585	-26.130	8.759
SPO2 - 3 Min	Equal variances assumed	10.282	.002	1.537	68	.129	.143	.093	-.043	.328
	Equal variances not assumed			1.537	34.000	.134	.143	.093	-.046	.332
SPO2 - 4 Min	Equal variances assumed	9.340	.003	1.435	68	.156	.057	.040	-.022	.137
	Equal variances not assumed			1.435	34.000	.160	.057	.040	-.024	.138
SPO2 - 5 Min	Equal variances assumed	4.634	.035	1.071	68	.288	.429	.400	-.370	1.227
	Equal variances not assumed			1.071	34.000	.292	.429	.400	-.385	1.242
SPO2 - 6 Min	Equal variances assumed	4.246	.043	1.000	68	.321	.200	.200	-.199	.599
	Equal variances not assumed			1.000	34.000	.324	.200	.200	-.206	.606
SPO2-Post Int	Equal variances assumed	4.246	.043	1.000	68	.321	.029	.029	-.028	.086
	Equal variances not assumed			1.000	34.000	.324	.029	.029	-.029	.087

DISCUSSION

Coronary artery bypass graft surgery (4) is done to revascularize the myocardium, in patients who have had previous myocardial injury, or the potential to sustain injury, resulting in a compromised myocardium that is prone to further injury.

Several factors during anaesthesia and surgery can tip over the delicate balance between myocardial demand and supply in these patients. Therefore, it is imperative that the surgical and anaesthetic techniques used for these patients are such that the myocardium is protected from further ischemia and injury. This is important as any peri-operative event can affect both immediate and late outcomes for the patient.

From the anaesthetic point of view, interventions for myocardial protection may be taken in the pre-bypass, bypass and post-bypass periods. Induction of anaesthesia, which falls in the pre-bypass period is the time of most haemodynamic instability- hypotension due to the sudden vasodilation caused by the anaesthetic agents, followed by tachycardia and hypertension caused by tracheal intubation.

When administering an anaesthetic to a cardiac patient, there are certain haemodynamic goals to be achieved (5). These are to reduce and control those factors that increase myocardial oxygen demand (high heart rate and high peripheral vascular resistance). At the same time, every attempt is made to optimize coronary blood flow (maintaining coronary perfusion pressure and increasing diastolic time). A smooth transition from consciousness to sleep is desired without untoward airway difficulties (ex: coughing, laryngospasm, truncal rigidity) or haemodynamic responses (hypotension from relative overdose, loss of sympathetic tone or myocardial depression; hypertension caused by airway insertion, laryngoscopy; tachycardia and bradycardia). Deep planes of anaesthesia, brief duration of laryngoscopy, and innumerable

pharmacological regimens have been proposed for the elimination of the hypertension and tachycardia associated with intubation of the trachea (6).

This study was a prospective, randomized, controlled trial comparing the effects of two Induction techniques- High dose Fentanyl and Multi-agent Combination induction with regard to haemodynamic stability in the induction phase of anaesthesia in patients undergoing Coronary Revascularisation Surgery. Our hypothesis was that High dose Fentanyl causes greater haemodynamic stability during this period, when compared to the Combination Technique.

High dose Fentanyl anaesthesia was first described in patients undergoing open heart surgery for cardiac valve repair (40, 41). It has been studied in doses ranging from 30 to 100µ/kg. Theodore H Stanley et al found High dose Fentanyl (50-100µ/kg) to be capable of producing complete anaesthesia and minimal changes in cardiovascular dynamics in patients with coronary artery disease (31). John M Murkin et al demonstrated that high dose fentanyl (50µ/kg) was capable of inducing anaesthesia rapidly and protecting against haemodynamic changes associated with tracheal intubation (32). J. Earl Wynands et al concluded that very high doses of Fentanyl (75µ/kg bolus followed by a 0.75µ/kg/min infusion) decrease the incidence of intra-operative hypertensive responses during coronary artery surgery, but they also stated that this decrease may be associated with post operative hypotension (33). Henry C. Hicks et al studied high- dose fentanyl at dosages of 15, 30 and 50µ/kg. They concluded that Fentanyl when used at doses above 30µ/kg caused myocardial depression, which they believed may be more pronounced in patients with low ventricular function (37).

The first objective of this study was to determine if the High dose Fentanyl induction regime which allowed avoidance of other agents like midazolam and sevoflurane which have the potential to cause hypotension, provided better haemodynamics during induction and intubation. In fact a study done by Heikkila et al has shown that an intravenous injection of a relatively low dose of midazolam during the induction of high-dose fentanyl anaesthesia seemed to be followed by rapidly increased venous pooling and a moderate to severe decrease in systemic arterial pressure (34).

This study showed that haemodynamic parameters, especially the systolic, diastolic and mean blood pressures were better maintained in the High dose group. In fact the systolic, diastolic and mean blood pressures were significantly lower in the Multi-agent group. This statistically significant difference is seen from the second minute of induction till 30 seconds post intubation (p-values < 0.05).

In comparison with the High dose group, the Multi-agent group's blood pressures seemed to be less well preserved. However, when observed in isolation, no blood pressure values are seen to be below a systolic of 90mmHg or below a mean of 60 mmHg. This is because, many of these patients in the Multi-agent group, had received multiple vasopressor bolus doses to aid in the maintenance of blood pressures above critical values. 20% received Ephedrine while 82.9% received Phenylephrine in the Multi-agent group when compared to 0% and 2.9% respectively in the High dose group. The blood pressures had actually dropped to below acceptable values in between the specific timed interval recording during beat-to-beat invasive pressure monitoring.

This study also demonstrated that the mean heart rates were significantly lower in the Multi-agent group when compared to the High dose Fentanyl group, especially from the 4th minute of

the 6-minute induction period, till 30 seconds post intubation (p values < 0.05). This was however not clinically significant because mean heart rate in this group never went below 59.7. The decrease in heart rate could be explained by the fact that more patients in this group received Phenylephrine when compared to the High dose group.

The second objective of this study was to measure the amount of vasopressor boluses required during the period of induction of anaesthesia. Our results showed that 7 patients required Ephedrine boluses in the Multi-agent group, when compared to nil boluses administered in the High dose Fentanyl group (20% vs 0%). Similarly 29 patients required Phenylephrine boluses in the Multi-agent group, while only one patient required it in the High dose Fentanyl group (97.1% vs 2.9%). These differences were statistically significant with p- values of 0.006 and < 0.001, respectively. From this we can conclude that a significant number of patients in the Multi-agent group required vasopressor support to maintain adequate blood pressures in the induction period. This is probably why the mean heart rate and blood pressure values in the Multi-agent group do not appear to be low enough to illustrate a haemodynamic instability, though they are statistically lower than the High dose Fentanyl group. Had these boluses not been given, a clinically significant change in heart rate and drop in blood pressures would have been apparent.

Another interesting feature is that there were a significantly higher number of patients with abnormal ECGs, and more importantly, low Ejection Fractions (EF < 50%) in the High dose Fentanyl group. The expected outcome would have been greater haemodynamic instability and higher requirement of vasopressor support in this group during induction. However the converse is seen. This supports our hypothesis that high dose Fentanyl does provide better haemodynamic

stability in cardiac induction even in these high risk patients. This finding is therefore in conflict with the theory of Henry C. Hicks et al, mentioned above (37).

Chest wall rigidity is a known complication of fentanyl, even at low doses. One study by P. Neidhart et al showed an incidence as high as 63% and 75% in two groups of patients, the former was given midazolam in addition to fentanyl. The appearance of rigidity was found to affect both cardiovascular and respiratory systems: central venous and pulmonary capillary wedge pressures showed a sharp increase in patients with fentanyl induced chest rigidity accompanied by CO_2 retention, due to an inability to ventilate these patients adequately. They concluded that small doses of midazolam do not prevent, but may attenuate, fentanyl induced chest wall rigidity and that the appearance of rigidity causes alterations of haemodynamic and respiratory variables during induction (35).

Considering that one of the most worrying aspects for the anaesthesiologist during a high dose fentanyl induction is the incidence of chest wall rigidity, our third objective was to look for the incidence of the same. This was done by looking at two parameters- a subjective difficulty in bag and mask ventilation and a drop in saturation. There was difficulty in bag and mask ventilation in only 2 patients in the High dose group, and this was not statistically significant (p- value = 0.246). There was also no statistically significant drop in saturation in the High dose Fentanyl group. This insignificant incidence of chest wall rigidity was probably because of a small priming dose of Vecuronium (0.2mg) given after the first 100µ of fentanyl during induction in the High dose group.

Therefore, we found that the High dose Fentanyl regimen provided greater haemodynamic stability with decreased vasopressor requirement during induction of anaesthesia in patients coming for coronary revascularization surgery.

Conclusion

In this randomized controlled study of 70 patients with coronary artery disease coming for coronary revascularization surgery, those in the High dose Fentanyl group exhibited better haemodynamic stability during induction of anaesthesia. This was shown by the absence of hypotension or bradycardia during induction, and the absence of hypertension or tachycardia after intubation. There was also a significant decrease in vasopressor bolus (Ephedrine and Phenylephrine) requirement, when compared to the Multi-agent group.

Incidence of chest wall rigidity among those in the High dose Fentanyl group was not significant.

Limitations

This study stopped with tracheal intubation, therefore haemodynamic parameters during the following events such as skin incision, sternal sawing etc. were not studied.

There were no other measures of myocardial ischemia such as ST segment changes or bio-chemical markers monitored.

Early extubation may not be possible in patients for whom High dose Fentanyl is used due to the possibility of delayed respiratory depression.

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APPENDIX – 1

Data Collection Sheet

HIGH DOSE FENTANYL VERSUS LOW DOSE FENTANYL+MIDAZOLAM+SEVOFLURANE FOR CARDIAC INDUCTION-DATA ENTRY SHEET

Patient Name: **Number:** **Weight:**

Ejection Fraction: **ECG:** **Drug list:**

ASA grade:

Drugs:_____μ Fentanyl; _____mg Midazolam; _____% Sevoflurane

Induction technique used: High dose Fentanyl/ Multi-agent Combination Technique

	Heart Rate (per min)	Blood Pressure (mm Hg)	O2 Saturation(%)
Baseline			
Induction 1minute			
2 minutes			
3 minutes			
4 minutes			
5 minutes			
30 sec after Intubation			

To treat hypotension if systolic BP is <90mmHg or mean BP is <60mmHg

USE OF EPHEDRINE (5/6mg boluses)

USE OF PHENYLEPHRINE (50/100mic boluses)

To treat hypertension if systolic BP is >130mmHg

USE OF GLYCERYL TRINITRATE (boluses/infusion)

Presence of Chest Wall Rigidity: Yes/ No

APPENDIX – 2

Data Entry Spread Sheet

S No.	Group	Name	Hosp No.	Sex	Age	Weight	Diabetes
1	1	SHEKHAR BHATTACHARYA	878195D	0	51	83	1
2	1	MD NISAMMUDDIN	523119D	0	38	72	0
3	1	ELDEN GELSON TERON	910188D	0	58	70	0
4	1	YASODHA	927626D	1	71	64	1
5	1	GAUTAM PRASAD PATEL	952812D	0	65	69	0
6	1	TAPAN SARKAR	846554D	0	59	50	1
7	1	THILAK	582553B	0	39	67	0
8	1	PHANI B DAS	877787D	0	64	57	0
9	1	SUREN PRADHAN	973489D	0	42	61	0
10	1	DEVANATHAN	927266D	0	60	70	1
11	1	INDU SINHA	896510D	1	73	73	1
12	1	DAMODAR MONDAL	907186D	0	44	56	0
13	1	MAYNA KUMAR ROY	895087D	0	58	60	1
14	1	PANEERSELVAM	901018D	0	47	63	0
15	1	MUNUSWAMY	895838D	0	61	82	0
16	1	NIMAI CHAND MANNA	903565D	0	53	60	0
17	1	SAMUEL VARGHESE	922375D	0	60	60	0
18	1	GOURANGA DAS	923593D	0	56	71	1
19	1	SHIV PRASAD SAHU	897808D	0	56	79	1
20	1	P CHATTERJEE	910650D	0	58	76	0
21	1	PANDURANGAN	247298D	0	64	65	0
22	1	KALYANI SAMANTA	859558D	1	55	65	0
23	1	MANI S	900045D	0	54	56	1
24	1	ALAKH NIRANJAN K	874648D	0	65	61	0
25	1	SAKAL DEV	944824D	0	60	64	0
26	1	UMAS CHANDRA A	940100D	0	52	55	0
27	1	CHAKRA BAHADUR	484414D	0	74	46	0
28	1	JANKI RANA	894822D	0	67	62	0
29	1	KIRAN JHA	988678C	1	47	64	1
30	1	GOPAL CHANDRA B	969544D	0	59	54	0
31	1	YUDISHTIR PAUL	957920D	0	59	60	0
32	1	PRABODH KUMAR ROY	964583D	0	57	60	0
33	1	C P SINGH	916582D	0	59	74	0
34	1	VENKATESAN	968098D	0	42	68	0
35	1	PERIATHAMBI	901435D	0	70	65	1
36	2	RAMANUJAM	175426D	0	59	71	1
37	2	PARESH CHANDRA	923409D	0	55	60	1
38	2	GURUNATH RAO	932543D	0	61	72	0
39	2	GEORGE T V	758373D	0	61	75	0
40	2	RAGHAW PRASAD	866569D	0	58	62	1
41	2	SAHADEV NANDI	872700D	0	66	61	0
42	2	GUNASEKARAN	901534D	0	51	46	1
43	2	BISHNU CHETTRI	286905D	0	60	69	0
44	2	SUGIA BIBI	893066D	1	60	50	0
45	2	NARAYANASWAMY	689114D	0	62	78	1
46	2	RENUGOPAL	810685B	0	60	63	1

Data Entry Spread Sheet

S No.	Group	Name	Hosp No.	Sex	Age	Weight	Diabetes
47	2	LOGANATHAN	817687D	0	42	66	1
48	2	VENKATESAN T	909922D	0	42	57	0
49	2	KASHI K	911796D	0	75	76	1
50	2	JAINUL MIYA	911477D	0	60	70	0
51	2	PITCHAI	878682D	0	51	83	0
52	2	CHINNA KANNAN	932528D	0	68	65	0
53	2	DASAVARTHAN	291688C	0	66	71	1
54	2	V KRISHNA MURTHY	910005D	0	73	71	0
55	2	KAMLA DEVI	897072D	1	60	52	0
56	2	PANKAJ ROY	928775D	0	59	65	0
57	2	RAJENDIRAN	788297D	0	51	52	1
58	2	ARUNAGIRI	862091D	0	63	58	0
59	2	SARJU PRASAD VERMA	793923D	0	35	59	0
60	2	MOHAMMED MONJU	947251D	0	31	76	0
61	2	KANTHA S	921467D	1	58	85	0
62	2	ANANTA BHATTACHARYA	888120D	0	69	58	1
63	2	RAMESH CHANDRA DEBNATH	931313D	0	56	65	1
64	2	SUNIL PATRA	903463D	0	53	77	0
65	2	PAUL CHELLA	918151D	0	56	54	1
66	2	KANNAN	352112D	0	51	74	0
67	2	RANU BALA MUDI	947270D	0	45	58	1
68	2	LAXMI GOSH	888438D	1	55	63	1
69	2	KUPPUSWAMY		0		63	0
70	2	RAGU	942287D	0	50	68	0

Data Entry Spread Sheet

S No.	COPD	HTN	CKD	PTCA	β Blocker	ACE Inhibitor	AR Blocker	CC Blocker
1	0	1	1	0	0	0	0	1
2	0	0	0	0	1	1	0	0
3	0	1	0	0	1	0	0	0
4	0	1	0	0	1	0	0	0
5	0	0	0	0	1	0	0	0
6	0	1	0	0	1	1	0	0
7	0	0	0	0	1	1	0	0
8	0	1	0	0	1	0	0	0
9	0	0	0	0	1	0	0	0
10	0	1	0	0	1	1	1	0
11	0	1	0	0	1	1	0	1
12	0	0	0	0	1	1	0	0
13	0	1	1	0	1	0	1	0
14	0	0	0	0	1	0	0	0
15	0	1	0	0	1	0	0	0
16	0	0	0	0	1	0	0	0
17	0	1	0	0	1	0	0	0
18	0	1	0	0	1	1	0	0
19	0	1	0	0	1	0	0	0
20	0	1	0	0	1	0	0	1
21	0	0	0	1	1	0	0	0
22	0	0	0	0	1	0	0	0
23	0	0	0	0	1	1	0	0
24	0	1	0	0	0	0	0	1
25	0	0	0	0	1	1	0	0
26	0	1	0	0	1	0	0	1
27	0	1	1	1	1	1	0	0
28	0	0	0	0	1	0	0	0
29	0	1	0	1	1	1	0	0
30	0	0	0	0	0	1	0	0
31	0	0	0	0	0	1	0	0
32	0	0	0	0	1	1	0	0
33	0	0	0	0	0	0	0	1
34	0	0	0	0	1	1	0	0
35	0	1	0	0	1	0	0	0
36	0	0	0	1	0	1	0	0
37	0	1	0	0	1	1	0	0
38	0	0	0	0	0	1	0	0
39	0	1	0	0	1	1	0	0
40	0	0	0	0	1	1	0	0
41	0	1	0	0	1	0	0	0
42	0	1	0	0	1	1	0	0
43	0	1	0	0	1	1	0	0
44	0	1	0	0	1	1	0	0
45	0	1	0	0	1	1	0	0
46	0	1	0	0	1	1	0	0

Data Entry Spread Sheet

S No.	COPD	HTN	CKD	PTCA	β Blocker	ACE Inhibitor	AR Blocker	CC Blocker
47	0	0	0	1	1	1	1	0
48	0	0	0	0	1	0	0	0
49	1	0	0	0	1	1	0	0
50	0	0	0	0	1	0	0	0
51	0	1	0	0	1	0	0	0
52	0	1	0	0	1	0	0	0
53	0	1	0	0	1	1	1	0
54	0	1	0	0	1	0	0	0
55	0	0	0	0	1	1	0	0
56	0	0	0	0	1	1	0	0
57	0	1	0	0	1	0	0	0
58	1	0	1	0	1	0	0	0
59	0	0	0	0	1	1	0	0
60	0	0	0	0	1	0	0	0
61	0	0	0	0	1	0	0	0
62	0	1	0	0	1	1	0	0
63	0	1	0	0	1	1	0	1
64	0	0	0	0	1	0	0	0
65	0	1	0	0	0	1	0	0
66	0	1	0	1	1	1	0	0
67	0	1	0	0	1	1	0	0
68	0	1	0	0	1	1	0	0
69	0	0	0	0	1	1	0	0
70	0	0	0	0	1	1	0	0

Data Entry Spread Sheet

S No	Nitrates	Digoxin	Diuretic	Anti-Anginal	EF	ECG	ASA grade	HR- Baseline
1	0	0	1	0	1	0	3	92
2	1	0	0	0	1	0	3	54
3	1	0	0	1	1	0	3	64
4	1	0	0	1	1	0	3	103
5	1	0	0	1	1	0	3	88
6	1	0	1	0	1	1	3	87
7	1	0	0	1	2	1	3	76
8	1	0	0	0	1	1	3	62
9	0	0	0	0	1	0	3	68
10	1	0	0	0	1	0	3	72
11	1	0	0	0	1	0	3	66
12	1	0	0	1	1	1	3	55
13	1	0	1	0	1	1	3	58
14	1	0	0	1	1	1	3	76
15	1	0	0	0	1	0	3	53
16	1	0	0	0	1	0	3	68
17	1	0	1	0	1	1	3	104
18	1	0	0	0	1	1	3	87
19	1	0	0	1	1	0	3	92
20	1	0	0	1	1	1	3	56
21	1	0	0	1	1	1	3	66
22	1	0	0	0	1	1	3	84
23	1	0	0	0	1	1	3	74
24	1	0	0	0	1	0	3	85
25	1	0	0	0	2	0	3	58
26	1	0	0	0	1	0	3	58
27	0	0	0	0	1	0	3	71
28	1	0	0	0	1	0	3	81
29	0	0	0	0	1	0	3	81
30	0	0	0	0	1	0	3	73
31	1	0	0	0	1	1	3	106
32	0	0	0	0	1	0	3	60
33	1	0	0	1	1	1	3	62
34	1	0	0	1	2	1	3	83
35	1	0	0	0	1	1	3	64
36	1	0	0	0	2	1	3	76
37	0	0	0	1	1	1	3	72
38	0	0	0	0	2	1	3	68
39	0	0	0	0	1	0	3	88
40	1	0	0	0	1	1	3	72
41	1	0	0	0	1	1	3	47
42	1	0	0	0	2	1	3	74
43	1	0	0	0	1	1	3	77
44	1	0	0	0	1	1	3	65
45	1	0	0	0	1	1	3	88
46	1	0	0	1	2	1	3	81

Data Entry Spread Sheet

S. No	Nitrates	Digoxin	Diuretic	Anti-Anginal	EF	ECG	ASA grade	HR- Baseline
47	0	1	1	1	3	1	3	75
48	0	0	1	1	1	1	3	80
49	1	0	1	1	2	1	3	75
50	1	0	0	1	1	1	3	59
51	1	0	0	0	1	1	3	64
52	0	0	1	0	1	1	3	70
53	0	0	1	1	2	1	3	84
54	1	0	0	1	1	0	3	80
55	0	0	0	0	2	1	3	93
56	1	0	0	0	2	1	3	86
57	1	0	0	0	1	1	3	64
58	1	0	1	0	1	1	3	81
59	1	0	0	0	2	0	3	82
60	0	0	0	0	1	0	3	59
61	1	0	0	1	1	1	3	68
62	1	0	0	0	0	1	3	57
63	1	0	0	0	2	1	3	70
64	1	0	0	1	2	1	3	72
65	0	0	1	0	1	1	3	90
66	1	0	0	0	2	1	3	70
67	1	0	0	0	1	0	3	75
68	1	0	0	0	2	1	3	60
69	1	0	0	1	2	1	3	103
70	0	0	0	0	2	1	3	90

Data Entry Spread Sheet

S No.	SBP -Baseline	DBP - Baseline	MAP-Baseline	SPO2-Baseline	HR- 1 Min	SBP - 1 Min
1	159	85	112	100	91	155
2	147	81	107	100	47	143
3	145	80	107	96	61	125
4	171	89	127	99	97	160
5	146	69	99	100	74	97
6	141	62	87	99	67	77
7	138	70	96	100	72	128
8	147	73	93	100	65	136
9	124	66	81	99	56	116
10	163	79	107	100	69	155
11	176	71	106	100	68	140
12	116	57	77	98	53	113
13	220	110	140	97	50	173
14	129	81	100	100	74	129
15	113	55	70	100	60	140
16	141	68	95	95	64	132
17	172	94	123	97	96	160
18	114	60	77	100	76	102
19	180	83	113	100	93	172
20	178	95	124	100	51	145
21	150	71	98	98	68	150
22	125	69	88	100	86	106
23	116	69	85	100	76	90
24	145	72	97	100	75	135
25	126	66	89	100	56	123
26	123	62	85	100	57	106
27	186	77	110	100	85	193
28	158	79	111	100	70	134
29	173	67	95	100	84	179
30	185	88	130	99	72	179
31	124	88	104	98	105	122
32	131	30	83	100	58	122
33	136	59	86	100	64	140
34	102	65	80	98	62	101
35	122	54	79	98	61	152
36	116	64	84	100	69	109
37	134	59	86	98	58	130
38	149	69	95	100	58	144
39	135	71	100	99	81	135
40	190	77	114	100	60	158
41	172	75	110	99	49	168
42	132	76	98	100	60	127
43	150	87	109	100	74	152
44	172	73	110	90	77	121
45	141	67	96	98	87	132
46	163	87	111	100	74	148

Data Entry Spread Sheet

S no.	SBP -Baseline	DBP - Baseline	MAP-Baseline	SPO2-Baseline	HR- 1 Min	SBP - 1 Min
47	105	54	74	99	72	106
48	137	80	101	100	77	142
49	118	69	88	97	74	119
50	150	75	100	100	57	157
51	150	87	113	100	58	142
52	160	80	107	100	66	153
53	105	61	74	100	81	104
54	152	66	95	93	81	122
55	168	74	108	100	83	169
56	111	72	89	99	84	116
57	108	63	81	100	65	100
58	192	77	115	100	70	170
59	151	87	108	100	77	148
60	133	82	102	100	58	134
61	142	90	107	95	57	110
62	181	61	102	100	60	180
63	127	49	75	98	76	147
64	129	76	89	100	58	124
65	123	70	89	100	79	114
66	121	71	85	100	60	116
67	117	62	80	100	64	107
68	139	61	87	100	54	120
69	140	82	104	100	109	125
70	150	82	104	100	92	146

Data Entry Spread Sheet

S No.	DBP - 1 Min	MAP - 1 Min	SpO2 - 1 Min	HR - 2 Min	SBP - 2 Min	DBP - 2 Min	MAP - 2 Min
1	85	112	100	88	107	67	81
2	77	102	100	51	132	73	94
3	69	87	100	57	100	57	73
4	80	110	100	81	107	59	73
5	50	66	100	71	75	41	52
6	42	53	100	60	107	53	71
7	72	91	100	69	118	56	79
8	67	89	100	57	96	51	64
9	64	82	100	57	117	68	85
10	76	102	100	70	133	70	93
11	58	85	100	55	114	50	70
12	64	81	95	54	107	61	77
13	70	104	100	46	148	63	89
14	78	92	100	66	97	61	70
15	58	85	100	55	111	53	72
16	61	87	100	53	105	52	72
17	86	115	100	84	120	68	83
18	55	69	100	72	59	31	39
19	80	111	100	69	128	70	84
20	83	97	100	50	117	67	81
21	72	96	100	64	101	58	72
22	66	88	100	79	79	50	59
23	55	68	100	74	86	50	58
24	69	91	100	83	126	68	90
25	64	85	100	57	95	49	60
26	55	70	100	60	90	44	59
27	82	118	100	67	145	67	95
28	67	92	100	73	113	57	73
29	77	103	100	59	107	49	68
30	92	124	100	65	139	74	99
31	87	101	100	98	98	73	84
32	63	84	100	60	107	58	76
33	62	90	100	58	102	45	63
34	64	77	100	62	93	58	69
35	72	103	100	66	134	63	88
36	60	77	100	68	105	62	79
37	62	84	100	59	121	61	81
38	66	94	100	61	140	66	89
39	70	91	100	86	111	62	80
40	64	93	100	64	124	54	77
41	75	107	96	47	167	74	107
42	70	93	100	58	124	74	94
43	86	111	100	73	137	85	103
44	58	82	100	70	154	69	99
45	66	89	100	82	113	56	75
46	73	94	100	65	158	89	116

Data Entry Spread Sheet

S No.	DBP - 1 Min	MAP - 1 Min	SpO2 - 1 Min	HR - 2 Min	SBP - 2 Min	DBP - 2 Min	MAP - 2 Min
47	54	71	100	67	116	58	78
48	79	103	100	60	129	72	93
49	71	87	99	70	119	74	91
50	78	102	100	50	147	71	96
51	78	100	100	57	146	85	109
52	74	100	100	66	156	75	102
53	62	77	100	78	98	58	72
54	58	72	100	66	106	59	75
55	70	106	100	75	126	51	74
56	75	90	100	81	106	68	84
57	60	78	100	60	117	65	85
58	70	103	100	68	143	74	97
59	84	104	100	90	155	94	114
60	85	104	100	57	142	93	111
61	70	83	100	59	107	65	79
62	64	100	100	45	145	50	79
63	62	94	100	65	142	62	92
64	70	87	100	58	108	72	84
65	66	83	100	74	104	62	77
66	70	81	100	70	114	67	84
67	51	71	100	63	102	50	68
68	54	76	100	52	116	50	72
69	73	94	100	79	110	66	80
70	81	104	100	90	146	82	102

Data Entry Spread Sheet

S No.	SPO2 - 2 Min	HR - 3 Min	SBP - 3 Min	DBP - 3 Min	MAP - 3 Min	SPO2 - 3 Min	HR - 4 Min
1	100	88	113	65	79	100	85
2	100	53	111	66	77	100	58
3	100	58	82	47	54	100	52
4	90	58	76	43	55	100	60
5	100	65	112	57	76	100	69
6	100	63	72	40	50	100	64
7	100	69	92	47	60	100	58
8	100	55	81	45	54	100	48
9	100	66	93	64	76	100	68
10	100	83	104	64	77	100	80
11	100	57	88	47	58	100	56
12	98	54	78	46	56	100	52
13	100	45	130	59	83	100	45
14	100	65	79	50	68	100	66
15	100	61	96	47	63	100	47
16	100	53	98	49	68	100	57
17	100	76	79	43	53	100	73
18	100	64	123	64	82	100	70
19	100	83	115	62	77	100	81
20	100	44	99	56	65	100	42
21	100	60	84	49	58	100	55
22	100	69	78	51	62	100	54
23	100	57	146	89	109	100	57
24	100	75	99	53	69	100	76
25	100	58	78	39	54	100	48
26	100	60	61	30	48	100	52
27	100	67	117	56	74	100	67
28	100	66	81	48	57	100	65
29	100	71	101	47	63	100	69
30	100	68	133	71	91	100	64
31	100	91	84	65	74	100	90
32	100	54	96	56	71	100	54
33	100	55	85	36	51	100	53
34	100	57	85	47	57	100	48
35	100	58	63	35	43	100	43
36	100	75	100	55	72	100	75
37	100	53	135	72	94	100	58
38	100	58	123	58	78	100	62
39	100	81	110	60	76	100	79
40	100	66	105	47	64	100	71
41	97	44	151	71	97	100	35
42	100	62	122	76	94	100	57
43	100	75	130	77	97	100	74
44	95	68	155	69	99	100	76
45	100	79	125	60	83	100	80
46	100	64	156	84	112	100	77

Data Entry Spread Sheet

S No.	SPO2 - 2 Min	HR - 3 Min	SBP - 3 Min	DBP - 3 Min	MAP - 3 Min	SPO2 - 3 Min	HR - 4 Min
47	100	68	121	61	81	100	63
48	100	88	130	83	102	100	99
49	100	69	113	67	85	99	72
50	100	55	136	69	91	100	63
51	100	58	150	88	112	100	60
52	100	69	158	79	105	100	69
53	400	76	88	52	63	100	77
54	100	75	113	59	78	97	76
55	100	75	120	56	77	100	86
56	100	85	103	67	82	100	80
57	100	63	125	67	89	100	62
58	100	68	137	55	82	100	68
59	100	83	142	85	104	100	81
60	100	49	128	84	99	100	64
61	100	59	97	65	76	100	68
62	100	47	131	52	76	100	53
63	100	70	145	64	93	100	72
64	100	60	121	69	87	100	62
65	100	84	98	66	75	100	83
66	100	71	105	59	73	99	70
67	100	63	104	47	68	100	62
68	100	51	112	54	73	100	51
69	100	83	106	66	80	100	94
70	100	78	145	84	103	100	77

Data Entry Spread Sheet

S No.	SBP - 4 Min	DBP - 4 Min	MAP - 4 Min	SPO2 - 4 Min	HR - 5 Min	SBP - 5 Min	DBP - 5 Min
1	102	59	74	100	87	98	56
2	112	64	81	100	60	99	57
3	100	65	79	100	51	105	64
4	111	54	78	100	54	120	59
5	94	50	65	100	73	86	44
6	98	54	69	100	61	101	54
7	96	56	74	100	55	103	60
8	120	65	85	100	45	136	61
9	117	69	83	100	66	100	57
10	96	58	71	100	78	93	58
11	107	55	80	100	55	130	59
12	88	60	71	100	45	106	64
13	111	53	73	100	45	105	52
14	80	52	61	100	68	68	44
15	145	71	96	100	45	133	65
16	78	40	54	100	60	91	52
17	63	35	47	100	72	93	53
18	114	58	76	100	71	107	56
19	98	55	70	100	82	87	50
20	75	43	51	100	42	109	66
21	67	40	53	100	52	69	39
22	98	58	73	100	51	101	55
23	125	71	88	100	61	106	58
24	101	52	68	100	75	88	50
25	112	59	78	100	49	92	45
26	85	49	61	100	52	89	51
27	108	53	69	100	65	87	46
28	96	63	79	100	62	121	65
29	88	40	55	100	66	145	85
30	117	63	80	100	62	111	61
31	65	51	58	100	75	80	62
32	76	44	56	100	55	92	54
33	86	38	54	100	54	96	43
34	103	66	78	100	54	90	54
35	112	63	81	100	43	133	64
36	109	58	76	100	77	106	57
37	144	72	98	100	60	145	75
38	134	66	89	100	64	140	68
39	96	53	67	100	78	100	60
40	140	57	80	100	71	140	56
41	149	71	96	100	43	111	57
42	128	76	96	100	55	128	76
43	137	81	99	100	77	126	76
44	143	65	95	100	67	143	66
45	112	56	74	100	81	105	51
46	150	80	105	100	74	154	78

Data Entry Spread Sheet

S No.	SBP - 4 Min	DBP - 4 Min	MAP - 4 Min	SPO2 - 4 Min	HR - 5 Min	SBP - 5 Min	DBP - 5 Min
47	129	68	89	100	75	147	82
48	154	92	110	100	99	156	93
49	112	68	84	100	75	117	72
50	128	65	86	100	70	134	70
51	150	91	113	100	71	142	85
52	164	79	107	100	64	162	78
53	72	40	50	100	75	79	47
54	111	57	73	99	76	115	61
55	137	60	91	100	87	139	63
56	93	60	74	100	75	91	58
57	120	65	85	100	63	123	67
58	127	51	76	100	68	121	53
59	148	88	107	100	80	139	79
60	121	81	95	100	66	128	85
61	100	57	71	100	64	96	56
62	140	52	79	100	54	142	52
63	151	65	97	100	71	150	64
64	133	73	93	100	64	136	78
65	126	75	91	100	88	133	75
66	104	59	72	99	70	105	60
67	122	49	78	100	65	106	45
68	114	56	75	100	53	120	58
69	120	78	96	100	88	130	78
70	131	74	94	100	82	125	70

Data Entry Spread Sheet

S No.	MAP - 5 Min	SPO2 - 5 Min	HR - 6 Min	SBP - 6 Min	DBP - 6 Min	MAP - 6 Min	SPO2 - 6 Min
1	70	100	89	97	56	69	100
2	70	100	60	93	55	67	100
3	78	100	52	82	50	62	100
4	79	100	53	101	51	68	100
5	60	100	70	84	46	59	100
6	70	100	61	95	50	67	100
7	59	100	64	88	50	64	100
8	83	100	45	115	54	74	100
9	69	100	66	97	56	68	100
10	69	100	78	103	62	74	100
11	80	100	56	128	56	78	100
12	78	100	51	100	56	72	100
13	71	100	46	107	52	71	100
14	53	100	67	67	45	55	100
15	86	100	46	123	60	82	100
16	68	100	59	90	49	65	100
17	68	100	70	100	61	74	100
18	73	100	72	98	52	67	100
19	60	100	81	97	55	71	100
20	79	100	42	122	59	79	100
21	48	100	54	87	52	64	100
22	71	100	52	95	52	67	100
23	75	100	64	95	60	63	100
24	66	100	74	107	62	78	100
25	62	100	51	82	40	55	100
26	64	100	55	87	49	60	100
27	58	100	65	103	52	71	100
28	85	100	65	95	65	75	100
29	108	100	66	142	61	86	100
30	77	100	63	111	61	77	100
31	70	100	71	71	51	60	100
32	68	100	54	105	62	76	100
33	60	100	55	85	35	50	100
34	63	100	59	72	45	53	100
35	87	100	45	118	54	74	100
36	75	100	74	105	57	72	100
37	100	100	60	149	73	103	100
38	90	100	65	125	59	80	100
39	70	100					100
40	78	100	68	141	58	80	100
41	73	100	46	118	60	78	100
42	96	100	54	124	70	91	100
43	91	100	74	135	79	96	100
44	95	100	68	130	62	85	100
45	68	100	80	101	49	67	100
46	105	100	76	156	81	108	100

Data Entry Spread Sheet

S No.	MAP - 5 Min	SPO2 - 5 Min	HR - 6 Min	SBP - 6 Min	DBP - 6 Min	MAP - 6 Min	SPO2 - 6 Min
47	107	100	76	143	78	103	100
48	117	100	99	158	95	119	100
49	87	100	78	126	72	91	100
50	91	100	67	136	71	92	100
51	106	100	76	159	89	117	100
52	106	100	57	138	67	91	100
53	58	86	71	74	41	52	93
54	79	100	74	114	60	77	100
55	91	100	87	136	60	87	100
56	71	100	74	100	64	75	100
57	88	100	62	124	67	89	100
58	76	100	68	120	53	75	100
59	98	100	78	133	76	94	100
60	101	100	66	129	86	102	100
61	69	100	63	89	52	64	100
62	76	100	54	145	53	78	100
63	97	100	73	148	63	95	100
64	96	100	65	131	75	90	100
65	94	100	89	140	76	94	100
66	75	99	70	106	62	76	100
67	70	100	66	107	51	73	100
68	79	100	51	116	59	78	100
69	99	100	81	143	87	108	100
70	90	100	82	125	69	88	100

Data Entry Spread Sheet

S No.	HR-Post Int	SBP-Post Int	DBP-Post Int	MAP-Post Int	SPO2-Post Int	Ephedrine	PNP
1	90	108	67	81	100	0	0
2	61	92	54	67	100	0	1
3	56	110	70	85	100	0	1
4	60	101	60	70	100	1	1
5	86	143	86	109	100	0	1
6	72	126	62	86	100	0	2
7	76	107	62	77	100	0	1
8	48	130	60	78	100	0	1
9	84	132	87	110	100	0	0
10	80	141	72	94	100	0	0
11	58	117	70	86	100	0	2
12	54	110	70	83	100	0	2
13	54	130	60	83	100	0	0
14	70	90	50	55	100	0	2
15	48	120	58	80	100	0	1
16	84	101	61	81	100	1	1
17	72	115	66	81	100	0	3
18	77	88	49	59	100	1	2
19	89	114	62	80	100	0	1
20	45	118	66	82	100	1	1
21	63	125	64	70	100	2	2
22	55	105	60	73	100	0	1
23	64	100	55	73	100	0	1
24	73	106	61	77	100	0	0
25	60	120	65	87	100	0	1
26	64	102	64	80	100	1	2
27	67	120	58	65	100	0	1
28	65	125	68	82	100	0	1
29	80	154	69	94	100	0	1
30	77	128	80	85	100	0	0
31	90	104	74	87	100	0	2
32	65	119	68	86	100	0	1
33	58	97	44	55	100	2	2
34	63	74	48	57	100	0	2
35	56	113	53	75	100	0	2
36	78	116	65	82	100	0	0
37	77	200	110	140	100	0	0
38	72	132	66	81	100	0	0
39	78	110	70	75	100	0	0
40	69	123	53	71	100	0	0
41	50	157	71	101	100	0	0
42	55	125	73	93	100	0	0
43	88	136	78	98	100	0	0
44					100	0	0
45	77	106	53	70	100	0	0
46	75	143	78	104	100	0	0

Data Entry Spread Sheet

S No.	HR-Post Int	SBP-Post Int	DBP-Post Int	MAP-Post Int	SPO2-Post Int	Ephedrine	PNP
47	80	147	82	103	100	0	0
48	102	161	98	122	100	0	0
49	76	125	66	88	100	0	0
50	71	147	76	100	100	0	0
51	80	170	93	123	100	0	0
52	52	122	55	77	100	0	0
53	79	104	68	80	100	0	2
54	76	117	60	83	99	0	0
55	87	141	63	90	100	0	0
56					100	0	0
57	65	129	69	91	100	0	0
58	70	140	80	100	100	0	0
59	78	130	74	95	100	0	0
60	74	150	94	115	100	0	0
61	64	103	65	78	100	0	0
62	55	133	49	74	100	0	0
63	81	151	65	99	100	0	0
64	69	131	68	92	100	0	0
65	86	146	74	97	100	0	0
66	70	116	67	83	100	0	0
67	76	112	59	82	100	0	0
68	56	123	59	80	100	0	0
69	84	150	90	110	100	0	0
70	99	119	69	85	100	0	0

Data Entry Spread Sheet

S No.	GTN	Atropine	CW Rigidity	OTHERS
1	0	0	0	α BLOCKER, SALBUTAMOL
2	0	0	0	84/49(59)
3	0	0	0	73/42(51)
4	0	0	0	E-96/52(56) P-81/43(56)
5	0	0	0	NIL
6	0	0	0	P2-84/44(55)
7	0	0	0	79/40(53)
8	0	0	0	NIL
9	0	0	0	NIL
10	0	0	0	NIL
11	0	0	0	NIL
12	0	0	0	P1-85/50(55) P2-78/46(56)
13	0	0	0	NIL
14	0	0	0	P1-79/55(70) P2-68/44(56)
15	0	0	0	86/60(55)
16	0	0	0	E-85/42(58) P-78/39(53)
17	0	0	0	NIL
18	0	0	0	NIL
19	0	0	0	NIL
20	0	0	0	NIL
21	0	0	0	E1-70/40(50) E2-70/40(50) P70/41(48)
22	0	0	0	NIL
23	0	0	0	NIL
24	0	0	0	NIL
25	0	0	0	NIL
26	0	0	0	P 86/43(55)
27	0	0	0	NIL
28	0	0	0	NIL
29	0	0	0	NIL
30	0	0	0	NIL
31	0	0	0	P1 71/53(61) P2 71/51(60)
32	0	0	0	P 76/44(56)
33	0	0	0	HYPOTHYROID ON REPLACEMENT
34	0	0	0	NIL
35	0	0	0	P1 63/35(44) P259/35(43)
36	0	0	0	NIL
37	0	0	0	NIL
38	0	0	0	NIL
39	0	0	0	NIL
40	0	0	0	NIL
41	0	0	0	NIL
42	0	0	0	NIL
43	0	0	0	NIL
44	0	0	0	NIL
45	0	0	1	NIL
46	0	0	0	NIL

Data Entry Spread Sheet

S No.	GTN	Atropine	CW Rigidity	OTHERS
47	0	0	0	NIL
48	0	0	0	NIL
49	0	0	0	NIL
50	0	0	0	NIL
51	0	0	0	NIL
52	0	0	0	NIL
53	0	0	1	FEV1:56.9 FVC 67.6 FEV1/FVC: 85.5
54	0	0	0	NIL
55	0	0	0	NIL
56	0	0	0	ON DERIPHYLLINE
57	0	0	0	NIL
58	0	0	0	ON SALBUTAMOL
59	0	0	0	NIL
60	0	0	0	NIL
61	0	0	0	NIL
62	0	0	0	NIL
63	0	0	0	NIL
64	0	0	0	NIL
65	0	0	0	NIL
66	0	0	0	NIL
67	0	0	0	NIL
68	0	0	0	NIL
69	0	0	0	NIL
70	0	0	0	NIL