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Recovery Profile Following General Anaesthesia with Isoflurane in Relation to Body Mass Index and Duration of Anaesthesia in Patients Undergoing Thyroidectomy

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Abstract: ***Background**: Increased BMI may increase the body's capacity to store potent inhaled anaesthetics, more so with more soluble agents. This study is intended to know whether increased BMI is associated with delay in recovery of verbal response, motor power and cognition after anaesthesia with Isoflurane. **Objectives**: Primary objective: To study recovery profile following general anaesthesia with isoflurane in patients undergoing total thyroidectomy. Secondary objectives: To study the effect of body mass index and to study the effect of duration of anaesthesia on recovery following anaesthesia with isoflurane. **Materials & Method**: This hospital based cross sectional study conducted at Dept of Anaesthesiology, Govt medical college, Trivandrum included a total of 96 patients undergoing total thyroidectomy under GA. Outcome variables measured are recovery time in terms of response to verbal commands, adequate motor power and cognition following anaesthesia with isoflurane. RESULTS: The correlation coefficient between BMI & recovery times are 0.51, 0.47& 0.45 respectively indicating moderate correlation. P value above is <0.001 suggesting that the correlation is highly significant. The correlation coefficient between DOA & recovery times are 0.01,0.033& 0.0 respectively indicating very weak correlation. P value above is > 0.05 suggesting that the correlation is not significant. **Conclusion**: From the present study it can be concluded that there is statistically significant (moderate) correlation between recovery times and BMI. Recovery times in patients with BMI>23Kg/m2 are prolonged as compared to that of with patients BMI<23 Kg/m2. There was no statistically significant correlation between DOA and recovery times.*

Keywords: Inhaled anesthetics; Isoflurane, Body Mass Index, Recovery times, Duration of anesthesia

1. Introduction

Inhaled general anesthetics were first used clinically more than 160 years ago. They soon became an intergral component of balanced anaesthesia.

Of all milestones and achievements in medicine, conquering pain must be one of the very few that has potentially affected every human being in the world. It was in 1846 that one of mankind's greatest fears, the pain of surgery, was eliminated when Dr W. T. G. Morton proved to the world that ether is a gas that when inhaled in the proper dose, provided adequate analgesia, safe and effective anaesthesia.

The general advantages of inhalation agents are more economical than injectables especially for long procedures, relies mainly in lung function for elimination, allows rapid changes in depth of anaesthesia . Postoperative recovery is rapid and less complicated than with injectable anaesthetics. Main disadvantages include the requirement of expensive equipments, operation theatre and environmental pollution.

The prevalence of obesity is escalating worldwide. For many Asian populations, additional trigger points for public health action were identified as 23 kg/m^2 or higher, representing increased risk, and 27·5 kg/m^2 or higher as representing high risk.

The suggested categories are as follows: less than 18·5 kg/m^2, underweight 18·5–23 kg/m^2, increasing but acceptable risk 23–27·5 kg/m^2, increased risk and 27·5 kg/m^2 or higher- high risk.[1]

Table 1: Nutritional status based on the WHO and "Asian criteria" values

Nutritional Status	WHO criteria BMI cut-off	"Asian criteria" BMI cut-off
Underweight	<18.5	<18.5
Normal	18.5 – 24.9	18.5 – 22.9
Overweight	25 – 29.9	23 – 24.9
Pre-Obese	-	25 – 29.9
Obese	≥30	≥30
Obese Type 1 (obese)	30 – 40	30 – 40
Obese Type 2 (morbid obese)	40.1 – 50	40.1 – 50
Obese Type 3 (super obese)	>50	>50

Increased BMI may increase the body's capacity to store potent inhaled anaesthetics, more so with more soluble agents[2]. In a prospective study of Lemmens HJ, Saidman LJ, Eger EI 2nd, Laster MJ on how obesity affects inhaled anesthetic kinetics in humans with 107 ASA physical status I-III patients observed that an increased BMI increases anesthetic uptake and, thus, the need for delivered anesthetic to sustain a constant alveolar anesthetic concentration, particularly with a more soluble anesthetic.[2]

In another study done by R. E. McKay, A. Malhotra1, O. S. Cakmakkaya, K. T. Hall1, W. R. McKay at Department of Anaesthesia and Perioperative Care, University of California San Francisco on the effect of increased body mass index and anaesthetic duration on recovery of protective airway reflexes after sevoflurane vs desflurane, by measuring the time from anaesthetic discontinuation until first response to command (T1); from response to command until ability to swallow (T2); and from anaesthetic discontinuation to recovery of ability to swallow (T3) in 120 patients within three BMI ranges in patients aged 18–75, undergoing surgery who received sevoflurane or desflurane, delivered via an LMA found that T1 and T3 after sevoflurane exceeded T1 and T3 after desflurane. Hence they concluded that Prolonged sevoflurane administration and greater BMI delay airway reflex recovery.

The contribution of BMI to this delay is more pronounced after sevoflurane than desflurane. [3,4,6,8,10-15]

Accordingly, this study is intended to know whether increased BMI is associated with delay in recovery of verbal response, motor power and cognition after anaesthesia with isoflurane.

Aims and Objectives

Aims of the study

To study the recovery profile following general anaesthesia with isoflurane in patients undergoing total thyroidectomy in terms of response to verbal commands, motor power and cognition following anaesthesia and to study the relation of body mass index and duration of anaesthesia on recovery.

Objectives

Primary objective

To study recovery profile following general anaesthesia with isoflurane in patients undergoing total thyroidectomy in terms of response to verbal commands, motor power and cognition following anaesthesia with isoflurane.

***Secondary objectives*:**

1) To study the effect of body mass index on recovery following anaesthesia with isoflurane.
2) To study the effect of duration of anaesthesia on recovery.

2. Review of Literature

Inhalational agents have played a pivotal role in anaesthesia history[16]. Modern anaesthesia is said to have began with the successful demonstration of ether anaesthesia by William Morton in October 1846. The first publicly demonstrated anaesthetic, diethyl ether, was an inhalational anaesthetic. The attributes of a good agent, ability to rapidly induce anaesthesia, with limited side effects has lead research efforts for over a hundred and fifty years. Anaesthesia with ether, nitrous oxide and chloroform (introduced in 1847) rapidly became common place for surgery. Of these, only nitrous oxide remains in use today .The explosion hazard was largely conquered with the development of the halogenated agents in the 1950s[17,18] . All modern volatile anaesthetics, with the exception of halothane (a fluorinated alkane), are halogenated methyl ethyl ethers. Methyl ethyl ethers are more potent, stable and better anaesthetics than diethyl ethers. Rapid emergence, with limited nausea and vomiting continue to drive discovery efforts, yet the „modern" agents continue to improve upon those in the past[17]. The future holds promise, but perhaps the most interesting contrast over time is the ability to rapidly introduce new agents into practice.

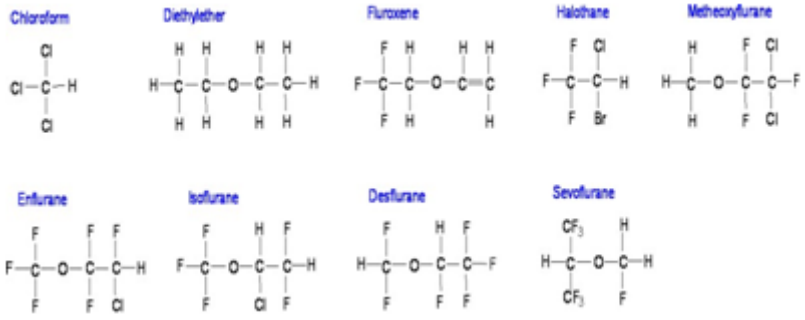

Figure 1: Chemical structure of inhaled anaesthetics

Table 2: Properties of inhaled anaesthetics

Agent	Formula	Molecular weight (Da)	Boiling point (°C)	SVP at 20 °C		Blood–gas solubility	MAC (in O_2) (%)	Metabolism (%)
				kPa	mmHg			
Halothane	$C_2HBrClF_3$	197.39	50.2	32.4	243.3	2.5	0.75	20
Enflurane	$C_3H_2CF_5O$	184.5	56.5	22.9	172	1.91	1.68	2.4
Isoflurane	$C_3H_2CF_5O$	184.5	48.5	33.2	250	1.4	1.15	0.2
Sevoflurane	$C_4H_3F_7O$	200.5	58.5	21.3	160	1.69	2	4
Desflurane	$C_3H_2F_6O$	168.04	22.8	88.3	664	0.42	6	0.02
Nitrous oxide	N_2O	44	−88	–	–	0.42	105	0
Xenon	Xe	131.3	−107.1	–	–	0.115	71	0

Throughout the second half of the 19th century the search continued for the ideal inhaled anaesthetic. The introduction of halothane, and subsequently enflurane and isoflurane, and the research that followed has identified which properties are desirable in a volatile anaesthetic agent[4] .

Table 3: *Properties of an ideal inhalational anaesthetic agent*[5]

- It should be cheap and easy to produce
- It should be chemically stable and not decompose on exposure to light or interact with anaesthetic circuits or soda-lime.
- It should have a long shelf-life without the addition of preservatives
- It should be nonflammable and non-explosive
- It should have a low blood-gas solubility, thereby allowing rapid induction, rapid recovery, and rapid alteration of depth of anaesthesia
- It should have a pleasant odor and not irritate the airway to facilitate inhalational induction
- It should be sufficiently potent to allow administration in conjunction with high concentrations of oxygen if necessary
- It should produce unconsciousness with some degree of analgesia and muscle relaxation
- It should cause no cardiovascular or respiratory depression and no central nervous system excitation
- It should have no organ toxicity and should not undergo any metabolism, being excreted completely unchanged by the lungs
- It should not cause histamine release or cause allergic reactions
- It should not trigger malignant hyperpyrexia
- It should not interact with other drugs

No agent currently available meets all the criteria, although several of the modern agents do combine many of them. Enflurane & isoflurane were two compounds were among 700 synthesized by Ross Terrell in the 1960s. Because enflurane, first synthesized in 1963, was easier to create, it preceded isoflurane. Enflurane use was restricted after it was shown to be a marked cardiovascular depressant and to have convulsant properties.

Isoflurane, first synthesized in 1965, was nearly abandoned because of difficulties in purification. After this problem was overcome by Louise Speers, several successful trials were published in 1971. The release of isoflurane for clinical use was delayed a second time when there calls for repeated testing in lower animals, due to concerns that the drug might be carcinogenic. As a consequence, isoflurane was the most investigated drug heretofore used in anaesthesia [18,19].

ISOFLURANE

Physical properties

Isoflurane is a structural isomer of enflurane[20] it is a halogenated methyl ethyl ether . It has a pungent ethereal odor, moderately irritating. The three fluorine atoms on the terminal ethyl carbon make it resistant to chemical or biological degradation.It is nonflammable, stable in ultraviolet light, and noncorrosive, and can be stored without a preservative at room temperature. Since it contains a CHF3 moiety and may undergo some degradation when exposed to dried soda-lime or Baralyme, resulting in the production of carbon monoxide.

The saturated vapor pressure is 250mmHg at *20 ^{O}C*, which is almost the same as that of halothane (243mmHg) . This means that halothane and isoflurane vaporizers could be used interchangeably with little loss in accuracy in the delivered concentration. For obvious reasons, this practice is not encouraged. Isoflurane is absorbed by the plastics and rubber found in anaesthetic circuits.[5] MAC decreases with increasing age, ranging from 1.28% in young adults down to 1.05% in patients over the age of 55 years. The MAC in middle-aged patients is 1.15%. The addition of 70% nitrous oxide roughly halves the MAC, which is also reduced by lidocaine (lignocaine), alcohol, and narcotic analgesics.[5] The MAC is also reduced by hypothermia ,a 5.3% fall for every degree drop in temperature. The MAC is not influenced by the duration of anaesthesia.

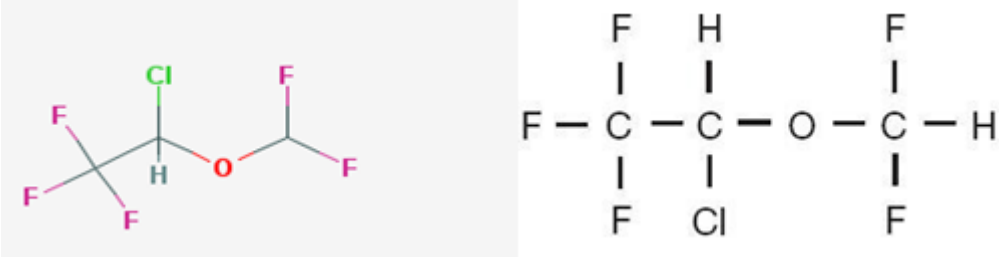

Figure 2: Isoflurane
1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether

Table 2: Properties of Isoflurane

Properties	Isoflurane
Fomula	CHF_2-O-CHCl-CF_3
Molecular weight	183.5
Boiling point (^oC)	48.5
SVP at 20 ^oC(mm Hg)	250
MAC	1.15
Blood gas solubility	1.4
Ordor	Pungent
Preservatives	None

Pharmacokinetics
Isoflurane has a lower blood-gas solubility which means that the inspired concentration and the alveolar concentration equilibrate more quickly. The use of higher initial concentrations to achieve a given alveolar concentration can compensate for the slow equilibration.

However, because of its pungency, rapidly increasing the inspired concentration of isoflurane during induction may induce coughing and breath-holding. This limits the rate of induction in patients breathing spontaneously. Pungency does not limit the rate at which anaesthetic depth is changed, and is not a problem during recovery, both of which should be quicker with isoflurane. A five-compartment model best describes the distribution of isoflurane. Isoflurane undergoes minimal metabolism in man, with less than 0.2% being recovered as urinary metabolites. Excretion is primarily through the lungs. Metabolism is by oxidation by hepatic cytochrome P450 2EI with the production of inorganic fluoride and trifluoroacetic acid.

Pharmacodynamics

Central nervous system effects
Isoflurane produces a dose-dependent depression of CNS activity. Concentrations above 0.25 MAC produce amnesia. The greatest reduction in cerebral oxygen consumption occurring at concentrations below 1 MAC. Cerebral oxygen consumption is reduced by 23% at 1 MAC and 30% at 2 MAC. Isoflurane is not associated with epileptiform activity, even at deeper levels of anaesthesia with profound hypocapnia. As the concentration of isoflurane increases towards 1 MAC there is an increase in the voltage amplitude and the frequency of the EEG [19]. At concentrations up to around 1 MAC,the voltage amplitude of the EEG continues to increase, but the frequency starts to decrease.

As anaesthesia deepens further, both frequency and amplitude start to decrease. At 1.5 MAC, burst suppression occurs, and at 2 MAC an isoelectric pattern appears. Concentrations of 1 MAC isoflurane also increase the latency of auditory evoked brainstem potentials.

Isoflurane does not increase CBF in normocapnic, normotensive patients in concentrations up to 1.1 MAC, but 1.6 MAC is associated with a doubling of CBF if blood pressure is maintained. If mean arterial pressure (MAP) is allowed to fall, CPP and cerebral blood flow are both reduced. Cerebral autoregulation is also impaired by isoflurane compared with propofol. In normocapnic patients without an intracranial mass lesion, isoflurane slightly increase lumbar CSF pressure compared with propofol. The increase in intracranial pressure that occurs with isoflurane is easier to reverse with hypocapnia than the increase that occurs with halothane. [20]

In hypocapnic neurosurgical patients with supratentorial mass lesions [end-tidal CO, 2.4-2.9kPa (l8-22mmHg)], concentrations of 1 MAC isoflurane were associated with no change in ICP. [21,22,40]

Respiratory effects
Isoflurane is quite irritating to the airway, and is not particularly well suited for inhalational induction. It causes slightly greater dose-related respiratory depression. Respiratory rate is increased and tidal volume is reduced, with a net reduction in minute ventilation. The ventilatory response to increasing *PaC02* is decreased with increasing concentrations, and approaches zero at 2 MAC. [23] The ventilatory response to hypoxemia is also impaired by isoflurane. Concentrations as low as 0.1 MAC can reduce it by up to 70%, and concentrations above 1.1 MAC abolish it completely. [23] Isoflurane seems particularly to depress the ventilatory responses mediated by peripheral chemoreceptors. [23] Isoflurane reduces functional residual capacity and pulmonary compliance at concentrations of 1MAC,with no further decrease at 2 MAC, and airways resistance is increased. [24]While studies with isolated lungs have shown that isoflurane reduces hypoxic pulmonary vasoconstriction, in the clinical situation this is not a significant problem.[25] Isoflurane does not increase airways resistance, and its use in patients with chronic asthma does not seem to cause any particular problems. [26]

Cardiovascular effects
Although in vitro studies have shown that isoflurane depresses the contractility of an isolated heart, clinically it is associated with minimal apparent myocardial depression at concentrations of up to 2 MAC, partly because of a fall in peripheral vascular resistance. Heart rate increases, stroke volume decreases, and cardiac output remains at awake

levels.[27]

Sudden exposure to high concentrations of isoflurane may be associated with tachycardia and a rise in blood pressure. Isoflurane causes a significant drop in peripheral vascular resistance, and hence blood pressure, although this can be reversed by surgical stimulation. While there is a reduction in tone in all vascular beds, there is a proportionally greater reduction in the vascular tone of the skin and muscle beds, and therefore an increase in blood flow to these areas. As a result of the fall in perfusion pressure, blood flow to the splanchnic area may fall. [28] There is a reduction in renal blood flow, glomerular filtration rate, and urine production.[28]

Ventricular work and myocardial oxygen consumption are reduced, thereby improving the oxygen supply-demand ratio of the heart. In addition, isoflurane is also a coronary vasodilator. Indeed, there is evidence in dogs that it may cause coronary steal, and this has been a cause of some concern.[28] Coronary steal occurs when blood is directed away from collateral-dependent myocardium to areas of normal flow as a result of coronary vasodilation. This can result in ischemia in the collateral- dependent area. The coronary vasodilation produced by isoflurane is mediated through adenosine triphosphate (ATP)-gated potassium channels (KATP) . [29] These channels are generally inhibited in the presence of normal intracellular ATP levels. When ATP levels fall, as they will during ischemia, these channels open. This causes hyperpolarization and a reduction in cellular activity. In vascular smooth muscle, muscle tone is reduced and blood flow is therefore increased. This contributes to the regulation of blood flow. These channels are distributed throughout the cardiovascular system, including the heart. In myocardial cells, activation of these channels results in reduced action potential duration, reduced calcium entry, and a reduction in contractility. This helps to protect the cell from the effects of ischemia . In addition to producing coronary vasodilation, KATP agonists have been shown to protect against the effects of myocardial ischemia and enhance recovery post ischernia.[30] There is now evidence that isoflurane may protect the myocardium from ischemia by a similar effect on KATP channels.[30]

Although recent research has focused on the potential protective effect of isoflurane on the heart during and after myocardial ischemia, all the currently used agents may offer protection against myocardial ischaemia. [31] It is likely that this protection is multifactorial and includes free radical inhibition , preservation of myocardial ATP concentrations, opening of KATP channels, and alteration in calcium flux. Although isoflurane causes some slowing of myocardial conduction, the cardiac rhythm is more stable .The doses of epinephrine required to produce arrhythmia in 50% of patients receiving 1.25 MAC isoflurane is three times the dose required in patients receiving 1.25 MAC halothane.[27,32]

Neuromuscular effects

It has no effect on twitch height, but does cause fade with repeated stimulation. The neuromuscular effect is dose related . Isoflurane also augments the effect of muscle relaxants. In this it is more potent than halothane but less potent than enflurane.[33] Shivering also occurs during emergence from isoflurane anaesthesia, and can be suppressed with meperidine.[34] Although this is often a thermoregulatory response to hypothermia, isoflurane may also cause clonus and tonic stiffening despite normal temperatures. [34,35]

Toxicity

Hepatotoxicity has been reported following isoflurane anesthesia, although not as frequently as with halothane or enflurane, despite isoflurane now being used more frequently.[36] This may be because isoflurane undergoes significantly less metabolism. The mechanism of the hepatotoxicity is probably a result of the TFA metabolite forming neoantigens, as occurs with halothane and enflurane, and possibly desflurane Fluoride ions are also produced by isoflurane metabolism, but only in clinically insignificant amounts because of the low rate of metabolism. Although renal blood flow, glomerular filtration rate, and urine flow are all reduced during isoflurane anaesthesia, this does not appear to cause any long-term adverse effects. There is no evidence for nephrotoxicity associated with isoflurane anaesthesia. Isoflurane is degraded by desiccated CO2 absorbers to produce carbon monoxide, although not to the same degree as enflurane or desfiurane.

Isoflurane is a trigger agent for malignant hyperthermia in susceptible patients.

Inhaled Anaesthetics - Uptake and Distrinution

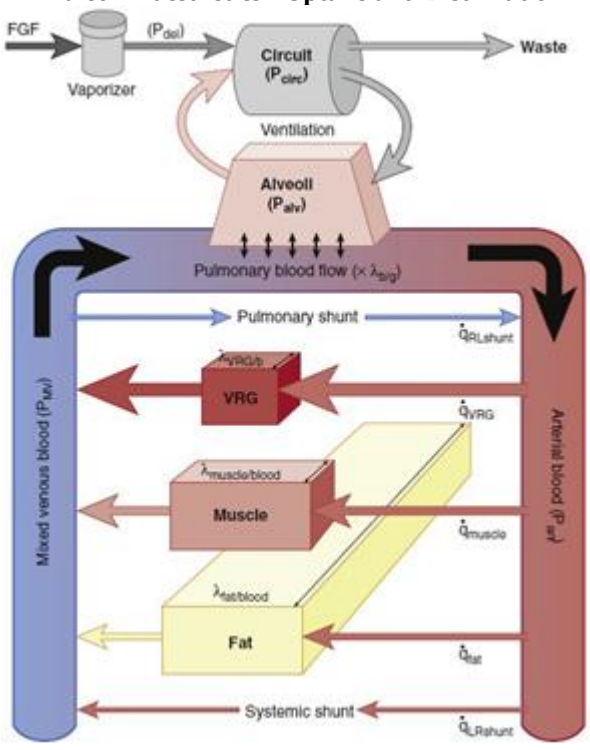

Figure 7: Flow diagram for uptake and distribution of inhaled anesthetics.

Three factors determine uptake of inhalational agent by blood: solubility (the blood-gas partition coefficient), pulmonary blood flow (cardiac output), and the difference in anaesthetic partial pressure between the lungs and venous blood returning to the lungs.[36]

Solubility differentiates one anaesthetic from another in that lower solubility translates to faster recovery from anaesthesia. The blood-gas partition coefficient (λ, or "blood solubility") describes the partitioning of an anaesthetic between blood and gas equilibrium which means that no difference in partial pressure exists.

For example, isoflurane has a blood-gas partition coefficient of 1.4, which means that at equilibrium, the concentration of isoflurane in blood is 1.4 times its concentration in the gas (alveolar) phase. Similarly it has a fat-blood partition coefficient of 45, which means that at equilibrium, the concentration of isoflurane in fat is 45 times its concentration in the blood.

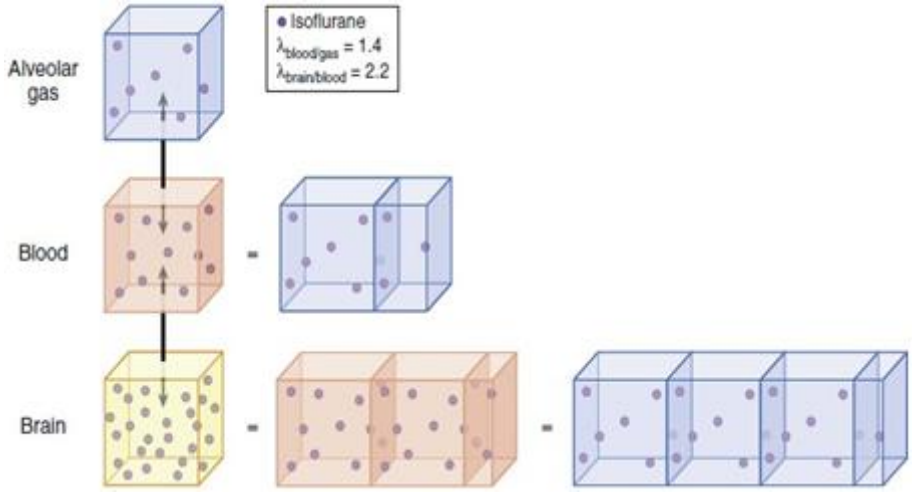

Figure 8: Partitioning of anaesthetic gases between different biophases

The algebraic sum of uptake by individual tissues determines the alveolar-to-venous partial pressure difference and hence uptake at the lungs [4].

Accordingly there is

1) Vessel rich group(VRG) including brain, heart, splanchnic bed (including the liver), kidney, and endocrine glands which accounts for less than 10% of body weight but receive 75% of cardiac output
2) Muscle group (MG) consisting ofmuscle and skin accounting for 50% of body mass and 19% of cardiac output.
3) Fat group contribute (FG) 20% of body mass and 6% of cardiac output.
4) Vessel-poor group (VPG) consists of ligaments, tendons, bone, and cartilage (i.e., lean tissues that have little or no perfusion). The absence of significant blood flow means that the VPG does not participate in the uptake process despite the fact that it represents a fifth of the body's mass (20%).

Table 4: Tissue group characteristics

	Group			
	Vessel Rich	Muscle	Fat	Vessel Poor
Percentage of body mass	10	50	20	20
Perfusion as a percentage of cardiac output	75	19	6	0

Once MG equilibration is complete, only fat (i.e., the fat group [FG]) serves as an effective depot for uptake. In a normal lean patient, the FG occupies a fifth of the body's bulk and receives a blood flow of about 400 mL/min (i.e., the perfusion per 100 cm^3 of fat nearly equals the perfusion per 100 cm^3 of resting muscle). Thus, during the initial delivery of anesthetic to tissues, the FG receives only 40% as much anesthetic as delivered to the MG (i.e., blood flow to the FG is 40% of that to the MG). The FG has far greater affinity than the MG for anesthetic, a property that greatly lengthens the time over which it absorbs anesthetic. The half-time to equilibration of fat ranges from 70 to 80 minutes for nitrous oxide to 30 hours for and isoflurane. Equilibration with fat does not occur in the course of anesthesia with any potent inhaled anesthetic.[38]

On recovery, the tissue partial pressures are variable. The VRG has a pressure that usually equals that required for anesthesia; that is, the VRG has come to equilibrium with the alveolar anesthetic partial pressure. The MG may or may not have the same partial pressure as that found in the alveoli. A longer anesthetic course (2 to 4 hours) might permit equilibrium to be approached, but a shorter one would not. The high capacity of fat for all anesthetics except nitrous oxide precludes equilibration of the FG with the alveolar anesthetic partial pressure until hours or even days after anesthesia.[38,39]

The failure of muscle and fat to equilibrate with the alveolar anesthetic partial pressure means that these tissues cannot initially contribute to the transfer of anesthetic back to the lungs. In fact, as long as an anesthetic partial pressure gradient exists between arterial blood and tissue blood, that tissue will continue to take up anesthetic. Thus, for the first several hours of recovery from anesthesia, fat continues to take up anaesthetic and by so doing accelerates the rate of recovery. Only after the alveolar (equals arterial) anaesthetic partial pressure falls below that in a tissue can the tissue contribute anaesthetic to the alveoli.

The failure of several tissues to reach equilibration with the alveolar anaesthetic partial pressure means that the rate of decrease in alveolar anaesthetic on recovery is more rapid than its rate of increase on induction and that recovery depends in part on the duration of anaesthesia. A longer

duration of anaesthesia puts more anaesthetic into the slowly filling muscle and fat depots. Obviously, these reservoirs can supply more anaesthetic to the blood returning to the lungs when they are filled than when they are empty and can thereby prolong the time to recovery.[40]

Solubility influences the effect of duration of anaesthesia on the rate at which the alveolar anaesthetic partial pressure declines.[39] The decline in partial pressure of a poorly soluble agent is rapid in any case, and thus the acceleration imparted by a less than complete tissue equilibration cannot significantly alter the rate of recovery. The approach to equilibration becomes important with increasing solubility. With a more soluble anaesthetic, recovery may be rapid after a short duration of anaesthesia but may be slow after a prolonged duration.[39]

Metabolism of Inhaled Anesthetics

Inhaled anaesthetics undergo varying degrees of biotransformation in various tissues[4]

Table 6: Metabolism of inhaled anaesthetics

Anesthetic	Halothane	Methoxyflurane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Extent of tissue metabolism (%)	25	70	2.5	0.2	0.02	5
Oxidating enzymes	CYP2E1, CYP2A6	CYP2E1, CYP1A2, 2C9/10, 2D6	CYP2E1	CYP2E1	CYP2E1	CYP2E1
Oxidative metabolites	F_3C-COOH, HBr, HCl	H_3C-O-CF_2-COOH, HCl_2C-COOH, HOOC-COOH, HF, HCl	HF_2C-O-CF_2-COOH, HCl, HF	HF_2C-O-CO-CF_3, F_3C-COOH, CF_2HOH, HCl	HF_2C-O-CO-CF_3, F_3C-COOH, CF_2HOH, HF	HO-$CH(CF_3)_2$, HF
Trifuoroacetylated hepatocellular proteins	+++++	n/a	++	+	+	none
Reducing enzymes	CYP2A6, CYP3A4	n/a	n/a	n/a	n/a	
Reductive metabolites	F^-, Br^- $F_2C=CHCl$ F_3C-CH_2Cl	—	—	—	—	—
Tissue toxicities	Hepatic	Renal, hepatic	Renal, hepatic	Hepatic	Hepatic	Hepatic
Fulminant hepatitis incidence	1:20,000	Reported, incidence unknown	1:300,000	Rare	Rare	Few case reports

The inhaled anesthetics are a unique group of drugs that can enter and leave the body unchanged through the lungs. Thus, chemical transformation of inhaled anesthetics is unrelated to their therapeutic activities, such as amnesia, hypnosis, and immobilization. Nonetheless, the carbon-halogen and other bonds of volatile alkanes and ethers can break down under certain conditions: biotransformation by enzymes in various tissues, reactions with strong bases in CO2 adsorbents, and exposure to ultraviolet radiation in the environment.Of the major organs involved in anaesthetic biotransformation, the liver and kidneys are exposed to the highest metabolite concentrations and thus are most susceptible to damage from toxic metabolites.

3. Materials and Methods

Study design

Hospital based cross sectional study

Study setting

Department of Anaesthesiology, Trivandrum

Duration of study

1year (Jan 2015- Jan 2016)

Study population

Patients undergoing total thyroidectomy under GA who satisfy inclusion and exclusion criteria.

Inclusion criteria

ASA PS 1 and 2 patients
Patients of age between 18-60 yrs.
Must give their informed written consent.

Exclusion criteria

Patients with neuromuscular disorder.
Patients with psychiatric disorder, mental retardation.
Patients with difficult airway.

Sample size calculation

Sample size was calculated using the formula N=(Z α)2 PQ /d2
where Z α is 1.96
P is the proportion of patients responded to verbal stimulus
Q is (100-P)
And d is 20% of P
A study done by R. E. McKay, A. Malhotra1, O. S. Cakmakkaya, K. T. Hall1,

W. R. McKay at Department of Anaesthesia and Perioperative Care, University of California San Francisco documented that protective airway reflexes appeared in 50% of study subjects in 2 minutes. This information is used to calculate sample size of the present study.
N= (1.96)2 50 X50/10 X10
=96

Sampling techniques

All consecutive patients eligible for study as per inclusion and exclusion criteria will be enrolled.

Study tool

Based on structured proforma

Study variables

Outcome variables- Recovery time in terms of response to verbal commands, adequate motor power and cognition

following anaesthesia with isoflurane

Time from isoflurane discontinuation until first response to verbal command(T1)(eye opening, tongue protrusion)
Time from isoflurane discontinuation until recovery of abitity to do motor activities(T2)(Head lift & hand grip)
Time from isoflurane discontinuation to recovery of cognitive functions (T3)(raising left/right arm-side specific).

Exposure variables- Body mass index, duration of anaesthesia, concentration of isoflurane administered.

Other variables-Age , gender, co-morbid illness, previous surgery, addictions.

Methods

After Research Methodology and Ethical Committee approval for the study, study subjects are selected from among those coming for thyroid surgery during the period of study at Medical college hospital. Subjects are assessed in the pre-anesthetic assessment clinic and categorized in to American Society of Anesthesiologists (ASA) physical status classes. Only patients belonging to ASA physical status 1 or 2 and satisfying the inclusion and exclusion criteria are considered for the study. Selected patients are asked about their willingness to participate in the study after explaining the details of the study to them. Both study subjects will receive T.Alprazolam 0.5mg and T.Pantoprazole on previous night before surgery and on morning of day of surgery.

Anaesthesia consists of premedication with midazolam 1mg ,ondansetron 4mg, glycopyrrolate 0.2mg with morphine given in a dose of 0.05-0.1mg/kg intra venously.

After induction of anaesthesia with propofol(1-2.5mg/kg),lignocaine1.5 mg/kg, neuromuscular blockade with vecuronium (0.1-0.2mg/kg), tracheal intubation is done. For maintenance of anaesthesia isoflurane is started at a concentration judged to be appropriate by the clinician between 0.4- 1% in oxygen 50% and nitrous oxide 50% with ventilation controlled to maintain end tidal carbon dioxide concentrations between 35 and 45 mmHg. Anaesthesia time (from start of anaesthesia with isolfurane upto its discontinuation) is noted. At the end of the procedure isoflurane is cut. Reversal of neuro muscular blockadeis done with neostigmine(0.05mg/kg) and glycopyrrolate (0.01mg/kg) and wait for respiration to become regular with adequate tidal volume. Once throat suction is given nitrous oxide is also cut and oxygenation is done with 100% oxygen alone and patients are asked repeatedly in normal tone of voice to open their eyes. Then recovery times (T1,T2 and T3) are noted.

Time from isoflurane discontinuation until first response to verbal command(T1) (eye opening ,tongue protrusion), Time from isoflurane discontinuation until recovery of abitity to do motor activities(T2) (Head lift & hand grip), Time from isoflurane discontinuation to recovery of cognitive functions (T3) (raising left/right arm-side specific).
BMI is calculated based on
Weight(Kg) /Height (m2)

For many Asian populations, additional trigger points for public health action were identified as 23 kg/m^2 or higher, representing increased risk. The suggested categories are as follows: less than 18·5 kg/m^2 underweight; 18·5–23 kg/m^2 increasing but acceptable risk; 23–27·5 kg/m^2 increased risk; and 27·5 kg/m^2 or higher high risk[1.]

Table 1: Nutritional status based on the WHO and "Asian criteria" values

Nutritional Status	WHO criteria BMI cut-off	"Asian criteria" BMI cut-off
Underweight	<18.5	<18.5
Normal	18.5 – 24.9	18.5 – 22.9
Overweight	25 – 29.9	23 – 24.9
Pre-Obese	-	25 – 29.9
Obese	≥30	≥30
Obese Type 1 (obese)	30 – 40	30 – 40
Obese Type 2 (morbid obese)	40.1 – 50	40.1 – 50
Obese Type 3 (super obese)	>50	>50

Cognitive functions which are intellectual process by which one becomes aware of, perceives, or comprehends ideas assessed by asking patient to raise right/left hand (side specific).

Statistical Analysis
Data were analyzed using computer software, Statistical Package for Social Sciences (SPSS) version 16. Qualitative data are expressed in proportion and percentage quantitative data expressed as mean and standard deviation. Associations and comparisons between different parameters is done using T test and correlation.

Interpretation of correlation
In statistical terms, correlation is used to denote association between two quantitative variables. It is assumed that the association is *linear*, that one variable increases or decreases a fixed amount for a unit increase or decrease in the other.

Correlation coefficient
The degree of association is measured by a correlation

coefficient, denoted by *r*. It is sometimes called Pearson's correlation coefficient after its originator and is a measure of linear association. If a curved line is needed to express the relationship, other and more complicated measures of the correlation must be used.

The correlation coefficient is measured on a scale that varies from 1 through 0 to 1. Complete correlation between two variables is expressed by either 1 or -1. When one variable increasesas the other increases the correlation is positive; when one decreases as the other increases it is negative. Complete absence of correlation is represented by 0.

To label the strength of the association, for absolute values of *r*, 0–0.19 is regarded as very weak,
0.2–0.39 as weak,
0.40–0.59 as moderate, 0.6–0.79 as strong, and
0.8–1 as very strong correlation, but these are rather arbitrary limits, and the context of the results should be considered.

For all statistical evaluations, a two-tailed probability of value, P <0.05 was considered significant.

Ethical considerations

- Institutional ethical committee clearance will be obtained.
- Data collection will be started only after getting ethical committee approval for the study.
- Informed written consent will be obtained from the participants.
- Confidentiality will be ensured and maintained throughout the study. Complications, if observed, will be dealt with accordingly.

4. Observations and Results

Over a period of one year, a sample of 96 patients undergoing total thyroidectomy under general anaesthesia all of whom satisfied the inclusion criteria were taken and were included in the study after obtaining proper informed written consent.

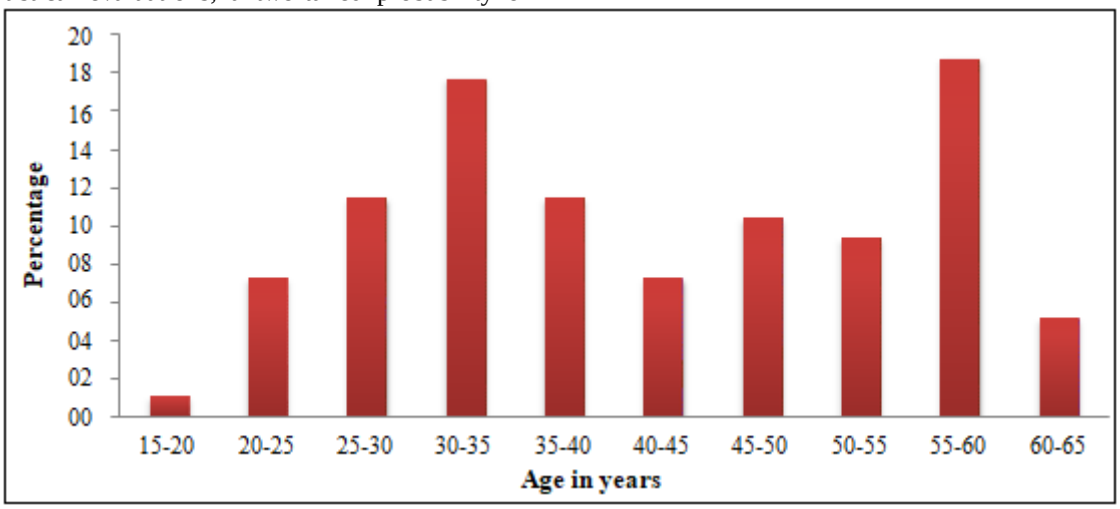

Figure 9: Distribution of age among the study population

In the study population, 18.75% patients are in the age group of 55-60, 17.71% are in the age group 30-35 &11.46% are in age groups 25-30 and 35-40 yrs. In the study population, the mean age is 41.68(SD 12.4). Minimum age is 19yrs and maximum age is 60 yrs.

Distribution of gender among the study population

Table 7: Distribution of study subjects according to the gender

	Frequency	Percent
Male	35	36.5
Female	61	63.5
Total	96	100.0

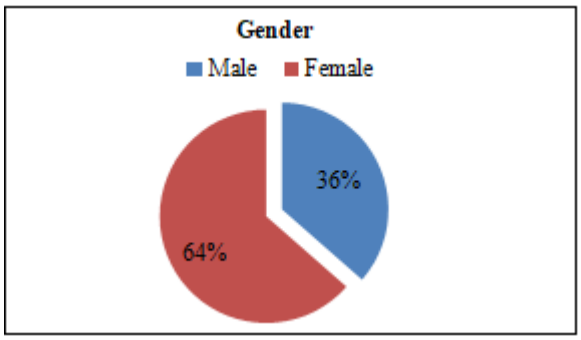

Figure 10

In the study population, 64% were females &36% were males.

Table 8: Distribution of study subjects according to age & gender

Age		
Male	N	35
	Mean	43.06
	Std. Deviation	11.402

	Minimum	21
	Maximum	60
Female	N	61
	Mean	40.89
	Std. Deviation	12.981
	Minimum	19
	Maximum	60

In the study population, mean age for men is 43.06 (11.4) and that for females is 40.9(SD12.9). Maximum and minimum age in males and females are 60& 21 and 60 & 19 respectively.

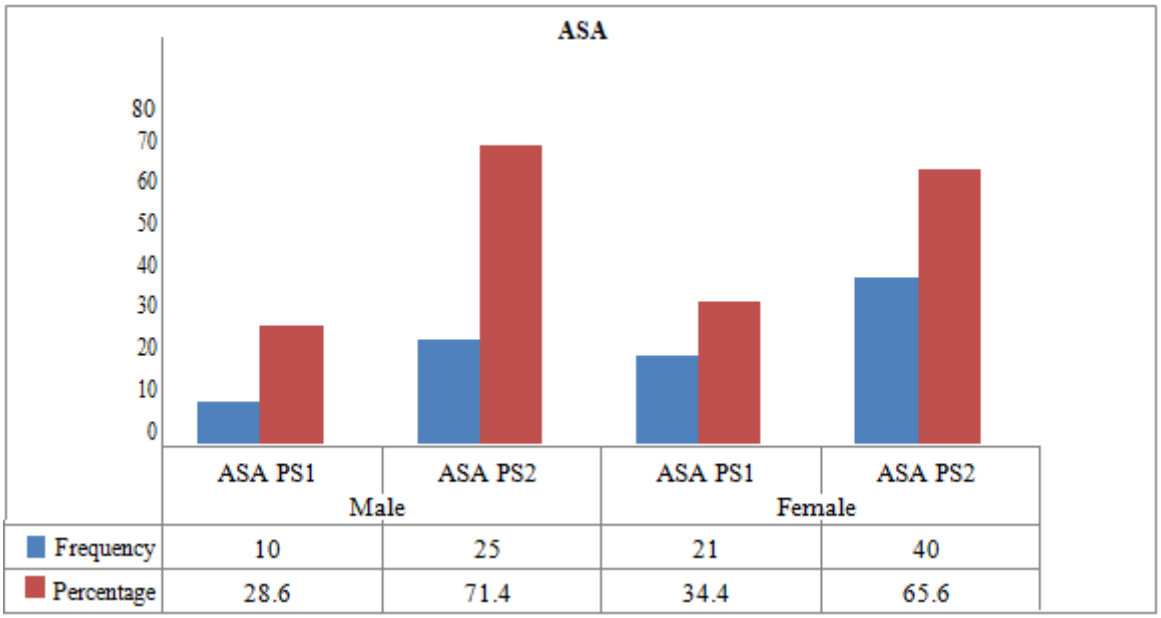

Figure 11: Distribution of subjects based on ASA PS category

In the study population, 32.3% patients are ASA PS1 and 67.7% are in ASA PS2

Table 9: BMI categories among the study subjects

BMI category	Gender		Total
	Male N(%)	Female N(%)	
<18.5 kg/m2	0 (0.0)	1 (1.6)	1 (1.1)
18.5-23 kg/m2	8 (23.5)	11 (18.0)	19 (20.0)
23 - 27.5 kg/m2	25 (73.5)	45 (73.8)	70 (73.7)
>27.5 kg/m2	1 (2.9)	4 (6.6)	5 (5.3)
Total	34 (100.0)	61 (100.0)	95 (100.0)

In the study population, 21.1% study subjects have BMI <23kg/m^2 and 79% have BMI>23Kg/m^2 .

Table 10: Distribution of BMI

N	96
Mean	24.5
Std. Deviation	1.87
Minimum	17.70
Maximum	28.30

Mean BMI of the study group is 24.5 kg/m2 with a standard deviation of 1.9. Minimum BMI is 17.7 & maximum BMI is 28.3.

Table 11: Comparison of the study subjects based on BMI

Sex		N	Minimum	Maximum	Mean	Std. Deviation
Male	BMI	35	22.06	28.20	24.5	1.55
Female	BMI	61	17.70	28.30	24.5	2.04

In the study population, mean BMI of males & females are 24.5 (1.6) and 24.5 (2.04) respectively.

Table 12: Distribution of the study subjects based on BMI

Presence of increased risk	Sex		Total
	Male	Female	
BMI <23 kg/m2	8 (23.5)	12 (19.7)	20 (21.1)
BMI 23 kg/m2 or above	26 (76.5)	49 (80.3)	75 (78.9)
	34 (100.0)	61 (100.0)	96 (100.0)

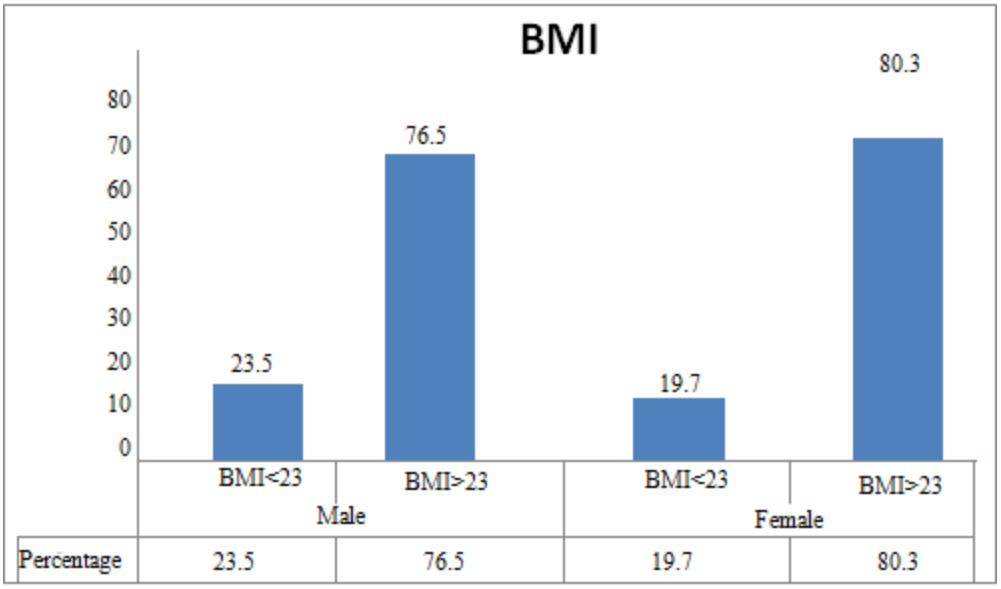

Figure 12: Distribution of the study subjects based on BMI

Table 13: Distribution based on presence of co-morbidities among the study subjects.

Name of the Diseases	Presence (Yes/No)	Gender		Total n(%)
		Male n(%)	Female n(%)	
DM	Yes	12 (34.3)	12 (19.7)	24 (25.0)
	No	23 (65.7)	49 (80.3)	72 (75.0)
HTN	Yes	14 (40.0)	18 (29.5)	32 (33.3)
	No	21 (60.0)	43 (70.5)	64 (66.7)
(Dyslipidemia) DLP	Yes	6 (17.1)	11 (18.0)	17 (17.7)
	No	29 (82.9)	50 (82.0)	78 (82.3)
Others(Asthma, CAD, PTB)	Yes	2 (5.7)	9 (14.8)	11 (11.5)
	No	33 (94.3)	52 (85.2)	85 (88.5)
Total		35 (100)	61 (100)	96 (100)

In the study population, 24% patients are diabetics, 32% are hypertensives. Dyslipidemia present in 17% study subjects.

Table 14: Distribution of study subjects based on habits .

Habits	Presence (Yes/No)	Gender		Total n (%)
		Male n(%)	Female n(%)	
Smoking	Yes	13 (37.1)	0 (0)	13 (13.5)
	No	22 (62.9)	61 (100)	83 (86.5)
Alcoholism	Yes	7 (20.0)	0 (0)	7 (7.3)
	No	28 (80.0)	61 (100)	89 (92.7)
Pan-chewing	Yes	1 (2.9)	0 (0.0)	1 (1.0)
	No	34 (97.1)	61 (100.0)	95 (99.0)
Total		35 (100)	61 (100)	96 (100)

Table 15: Distribution of duration of anaesthesia DOA (in min)

N Valid	96
Mean	61.03
Median	60.00
Std. Deviation	7.897
Minimum	48
Maximum	90

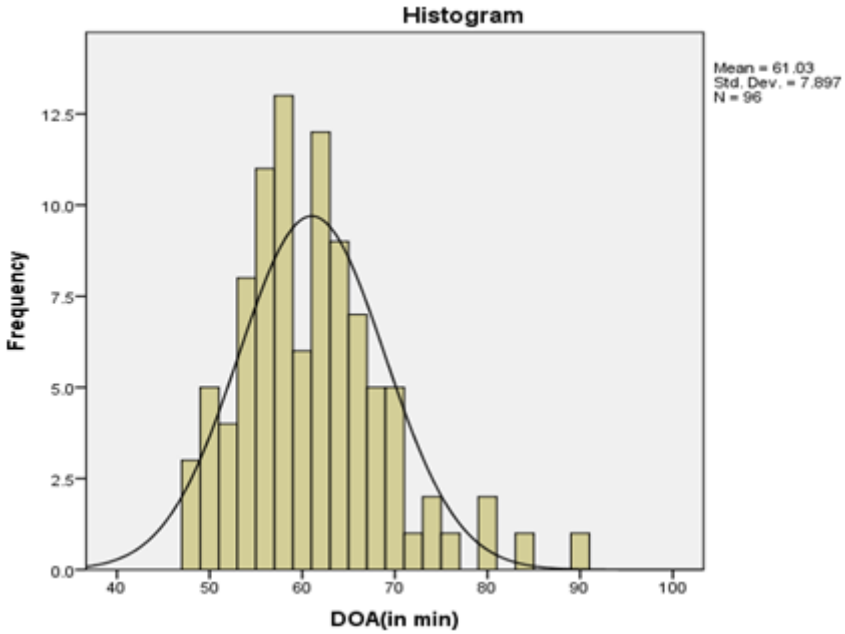

Figure 13: Distribution of duration of anesthesia DOA (in min)

In the study population, the mean duration of anaesthesia is 61 min (SD7.9). Minimum and maximum DOA are 48 minutes & 90 minutes respectively.

Table 16: Mean duration of Anaesthesia and recovery times among the different BMI categories.

BMI Category	DOA (in min)*	T1 in min*	T2 in min*	T3 (in min)*
BMI <23 kg/m^2	60.0 (6.2)	4.5 (1.3)	5.8 (1.7)	7.0 (2.3)
BMI 23 kg/m^2 or more	61.3 (8.3)	5.8 (1.7)	7.1 (1.9)	8.6 (2.3)

In the study population, mean(sd) of recovery times in patients with BMI>23Kg/m2 5.8, are T1 5.8(1.7)T2 7.1 (1.9) and T3 8.6 (2.3) are prolonged as compared to that of with patients BMI<23 Kg/m2- T1 4.5 (1.3),T25.8 (1.7) &T37.0 (2.3). This difference was found to be significant.

Table 17: Comparison of recovery times between two BMI groups

	BMI group	N	Mean	Std. Deviation	P-value
T1 (in min)	BMI <23 kg/m2	20	4.5	1.3	0.002
	BMI 23 kg/m2 or Above	75	5.8	1.7	
T2 (in min)	BMI <23 kg/m2	20	5.8	1.7	0.008
	BMI 23 kg/m2 or Above	75	7.1	1.9	
T3 (in min)	BMI <23 kg/m2	20	6.9	2.4	0.006
	BMI 23 kg/m2 or Above	75	8.6	2.3	

Table 18: Correlation between BMI and different recovery times

		T1 (in min)	T2 (in min)	T3 (in min)
BMI	Pearson Correlation	0.512**	0.467**	0.448**
	Sig. (2-tailed) P Value	<0.001	<0.001	<0.001

** Correlation is significant at the 0.01 level (2-tailed).

In the study population, the correlation coefficient between BMI & recovery times-Time from isoflurane discontinuation until first response to verbal command(T1)(eye opening, tongue protrusion) , time from isoflurane discontinuation until recovery of abitity to do motor activities(T2) (Head lift & hand grip),time from isoflurane discontinuation to recovery of cognitive functions (T3) (raising left/right arm-side specific) are 0.51,0.47 &0.45 respectively indicating moderate correlation. P value is <0.001 suggesting that the correlation is highly significant.

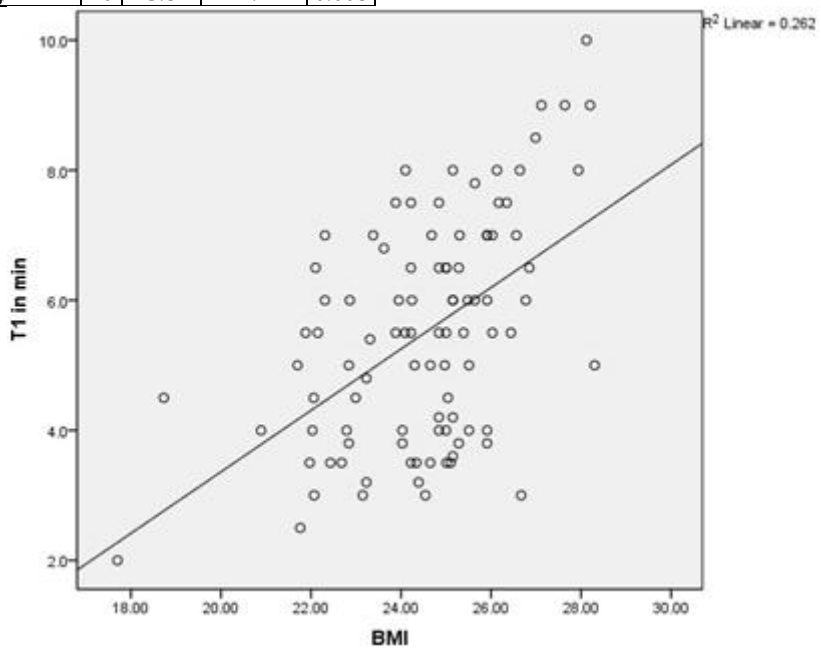

Figure 14: Correlation between BMI and recovery time T1

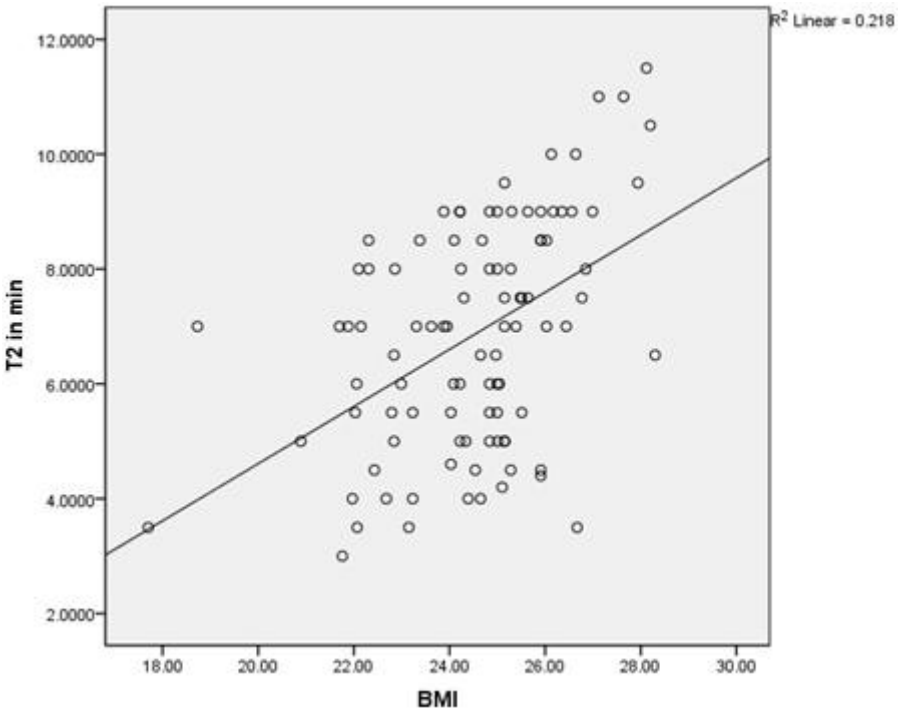

Figure 15: Correlation between BMI and recovery time T2

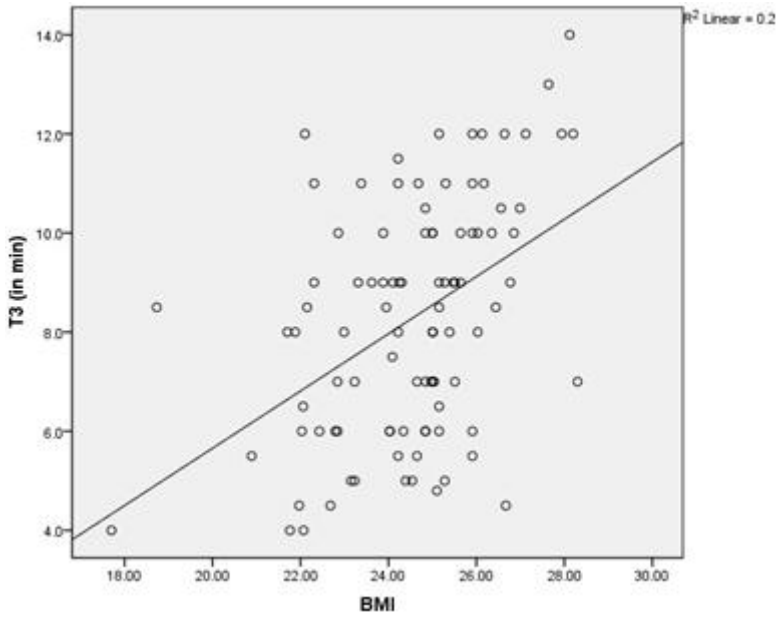

Figure 16: Correlation between BMI and recovery time T3

Table 19: Comparison between BMI and DOA

BMI Cut off	DOA(in min)
<23 Kg/m2	
Mean	60
SD	6.245
Minimum	48
Maximum	75
>23 Kg/m2	
Mean	61.32
SD	8.315
Minimum	48
Maximum	90

In the study population, the mean DOA in patients with BMI<23 kg/m2 is 60 min(6.2) and that in patients with BMI> 23kg/m2 is 61.3min (8.3).

Table 20: Correlation between duration of anesthesia and different recovery times

		T1 in min	T2 in min	T3 (in min)
DOA (in min)	Pearson Correlation	.007	.033	.000
	Sig. (2-tailed)	.948	.750	1.000

**. Correlation is significant at the 0.01 level (2-tailed).

In the study population, the correlation coefficient between DOA & recovery times-Time from isoflurane discontinuation until first response to verbal command(T1)(eye opening, tongue protrusion), time from isoflurane discontinuation until recovery of ability to do motor activities(T2)(Head lift & hand grip),time from isoflurane discontinuation to recovery of cognitive functions

(T3)(raising left/right arm-side specific) are 0.007,0.033& 0.0 respectively indicating very weak correlation. P value is > 0.05 suggesting that the correlation is not significant.

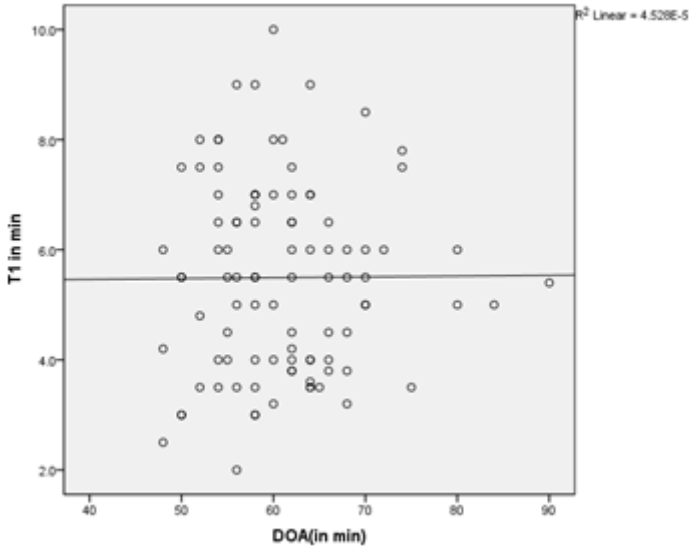

Figure 18: Correlation between Duration of anaesthesia and recovery time T1

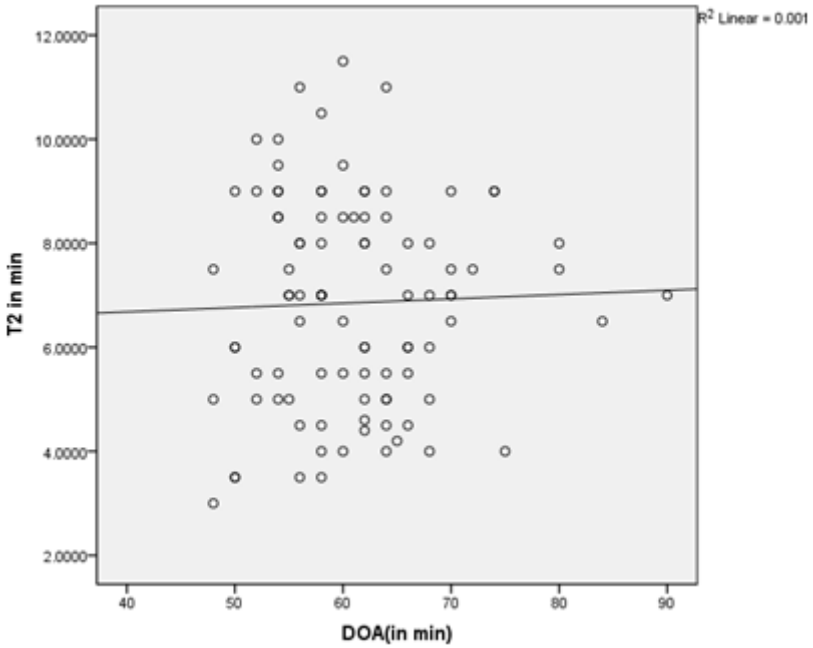

Figure 19: Correlation between Duration of anaesthesia and recovery time T2

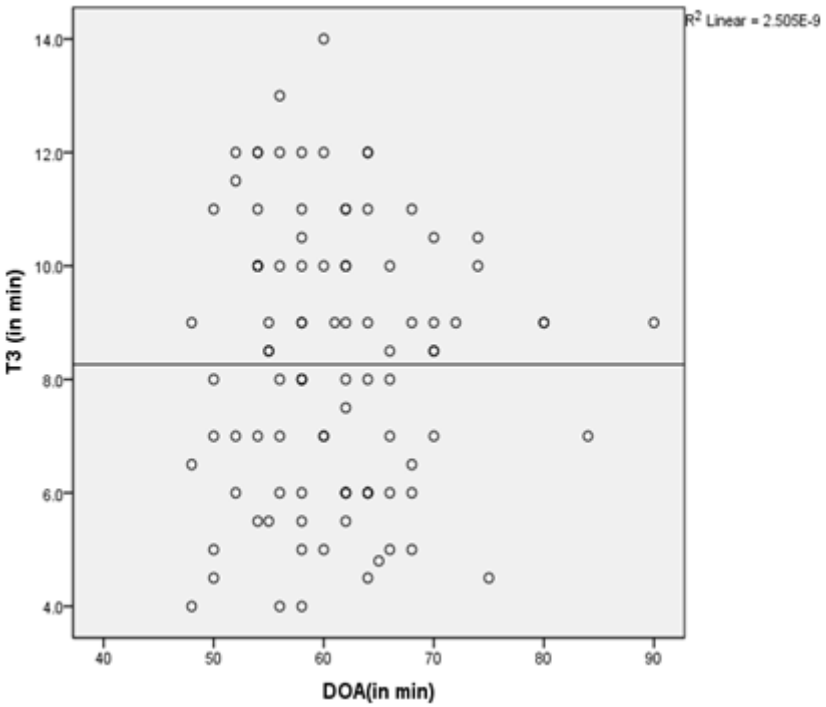

Figure 20: Correlation between Duration of anaesthesia and recovery time T3

Table 21: Correlation between Recovery time with BMI and Duration of anaesthesia

Variables (Recovery times)	BMI Pearson Correlation	P-value	DOA Pearson Correlation	P-value
T1	0.512	<0.001	0.007	0.948
T2	0.467	<0.001	0.033	0.750
T3	0.448	<0.001	0.000	1.000

5. Discussion

The prevalence of obesity is escalating worldwide.[2] In the United States 32% of adults are obese (BMI>= kg/m^{2}30), and almost 5% of the population are morbidly obese (BMI >=40). For many Asian populations, additional trigger points for public health action were identified as 23 kg/m2or higher, representing increased risk, and 27·5 kg/m2or higher as representing high risk. [1]

Although it is assumed that obesity may delay recovery, particularly from a lengthy anesthesia, [95] it is not clear how changes associated with obesity (such as distribution of fat and increased lean mass) affect the pharmacokinetics of inhaled anesthetics for ordinary durations of anesthesia. Tissue blood flow, and blood/gas and tissue/blood (tissue solubility) partition coefficients, are primary determinants of inhaled anesthetic uptake. In normal subjects, blood flow to fat accounts for only 5% of the cardiac output. [4] Furthermore, blood flow per kg of fat tissue decreases with increasing obesity and perfusion to fat may equal only 2% of cardiac output in morbidly obese patients.[96,97] In addition to uptake determined by anesthetic delivery in blood to tissues, as described using classic physiologic models,[97] a significant component of the uptake of inhaled anesthetics into fat tissue may occur by intertissue diffusion. Intertissue diffusion may move anesthetic from more rapidly equilibrating, highly perfused tissues such as kidney and other abdominal organs, into a thin sheet of adjacent fat, such as perirenal fat and omentum or mesenteric fat.[98]Intertissue diffusion might prolong the time to equilibrium between blood and highly perfused tissues acting, in effect, to increase the anesthetic capacity of these tissues.The small amount of fat receiving anesthetic by intertissue diffusion may consume a large amount of anesthetic and might equilibrate more rapidly than bulk fat.

The present study was undertaken to determine the recovery profile following general anaesthesia with isoflurane in relation to body mass index and duration of anaesthesia in patients undergoing total thyroidectomy The study was conducted in the Department of Anaesthesiology, Government Medical College Hospital Thiruvananthapuram, after obtaining approval of the research committee and human ethical committee and the duration of study was 1 year. The study population *included*

ASA PS 1 and 2 patients undergoing total thyroidectomy under general anaesthesia, of age between 18-60 yrs who gave their informed written consent. In this study recovery time in terms of response to verbal commands, adequate motor power and cognition following anaesthesia with isoflurane are observed in terms of time from isoflurane discontinuation until first response to verbal command(T1)(eyeopening, tongue protrusion)., time from isoflurane discontinuation until recovery of abitity to do motor activities(T2)(Head lift & hand grip), time from isoflurane discontinuation to recovery of cognitive functions (T3)(raising left/right arm-side specific).

A study done by R. E. McKay, A. Malhotra1, O. S. Cakmakkaya, K. T. Hall1, W.McKay at Department of Anaesthesia and Perioperative Care, University of California San Francisco studied 120 patients (60 receiving sevoflurane and 60 receiving desflurane) aged 18–75, in BMI ranges 18–24, 25–29, and >=30 kg/m2, undergoing surgery for which an LMA was the planned method of airway management, and randomly assigned these patients

to receive sevoflurane or desflurane.[3] Outcomes measured were: (i) time from anaesthetic discontinuation until first response to command (T1; recovery of consciousness); (ii) time from first response to command until first demonstrated ability to swallow (T2); and (iii) time from anaesthetic discontinuation until first demonstrated ability to swallow (T3). They observed that T1 and T3 after sevoflurane exceeded T1 and T3 after desflurane: 6.6 (SD 4.2) vs 4.0 (1.9) min (P< 0.001), and 14.1 (SD 8.3) vs 6.1 (2.0) min (P<0.0001). T3 correlated more strongly with BMI after sevoflurane (28 s per kg/ m2, P value= 0.02) than desflurane (7 s per kg/m2, P value= 0.03). Regarding T2, patients receiving sevoflurane with BMI 30 kg/ m^2 were less often able to swallow 2 min after response to command than were those with BMI 18–24 or 25–29 kg m22 (3/20 vs 10/20 or 9/20, P,0.05). It was concluded that prolonged sevoflurane administration and greater BMI delay airway reflex recovery. The contribution of BMI to this delay is more pronounced after sevoflurane than desflurane.

In a prospective study ofLemmens HJ, Saidman LJ, Eger EI 2nd, Laster MJ on how obesity affects inhaled anesthetic kinetics in humans with 107 ASA physical status I-III patients observed that an increased BMI increases anaesthetic uptake and, thus, the need for delivered anesthetic to sustain a constant alveolar anesthetic concentration, particularly with a more soluble anesthetic.[2,95]

In the study population, the mean age is 41.68(SD 12.4). Minimum age is 19yrs and maximum age is 60yrs of which 64% were females &36% were males.

The mean age for men is 43.06 (11.4) and that for females is 40.9(SD12.9). 32.3% patients are ASA PS1 and 67.7% are in ASA PS2.

Mean BMI of the study group is 24.5 kg/m2 with a standard deviation of 1.9. Minimum BMI is 17.7 & maximum BMI is 28.3. 76.5% males & 80.3% of females have BMI >23 kg/m^2 and 23.5% males & 19.7 % females have BMI<23 kg/m^2 The mean duration of anaesthesia is 61 min (SD7.9). Minimum and maximum DOA are 48 minutes & 90 minutes respectively.
In the study population, mean(SD) of recovery times in patients with BMI>23Kg/m2 are T1 5.8(1.7)T2 7.1 (1.9) and T3 8.6 (2.3) are prolonged as compared to that of with patients BMI<23 Kg/m2- T1 4.5 (1.3),T25.8 (1.7) & T3 7.0 (2.3).

In the study population, the correlation coefficient between BMI & recovery times-Time from isoflurane discontinuation until first response to verbal command(T1)(eye opening, tongue protrusion) , time from isoflurane discontinuation until recovery of abitity to do motor activities(T2)(Head lift & hand grip),time from isoflurane discontinuation to recovery of cognitive functions (T3)(raising left/right arm-side specific) are 0.512,0.467&0.448 respectively indicating moderate correlation. P value is <0.001 suggesting that the correlation is highly significant. This is comparable with results of A study done by R. E. McKay, A. Malhotra1, O. S. Cakmakkaya, K. T. Hall1, W. R. McKay at Department of Anaesthesia and Perioperative Care, University of California San Francisco.[3,2,100]

In the study population, the mean DOA in patients with BMI<23 kg/m2 is 60 min(6.2) and that in patients with BMI> 23kg/m2 is 61.3min (8.3).

In the study population, the correlation coefficient between DOA & recovery times-Time from isoflurane discontinuation until first response to verbal command(T1)(eyeopening ,tongue protrusion) , time from isoflurane discontinuation until recovery of abitity to do motor activities(T2)(Head lift & hand grip),time from isoflurane discontinuation to recovery of cognitive functions (T3)(raising left/right arm-side specific) are 0.007,0.033& 0.0 respectively indicating very weak correlation. P value above is > 0.05 suggesting that the correlation is not significant.

6. Limitations of the Study

- The sample size of the study was kept at the minimum required ,as the sampling method was non random sampling.
- A larger sample size should have been recruited. Inhalational agents were delivered as per dial concentration. Gasman analysis could have been used with which actual quantity of agent used can be measured.
- Study setting is a tertiary care centre, where complicated cases are referred from the lower levels of health care. Hence the results obtained may be over exaggerated.

7. Conclusions

From the present study it can be concluded that there is statistically significant (moderate) correlation between recovery times (T1,T2 and T3) and BMI. Recovery times in patients with BMI>23Kg/m^2 are prolonged as compared to that of with patients BMI<23 Kg/m^2.

There was no statistically significant correlation between Duration Of Anaesthesia and recovery times .

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