Benghazi University

Faculty of Medicine

EFFECTS OF SEVOFLURANE ANESTHESIA ON HEPATIC AND RENAL FUNCTION ON PATIENT UNDERGOING LENGTH OPERATION

" A dissertation submitted in partial fulfillment for the requirement for the degree of master of science in biochemistry to the faculty of medicine, Benghazi university, Benghazi, Libya"

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ABSTRACT

Sevoflurane is an inhalation anaesthetic agent degradation by carbon dioxide absorbents during low flow anesthesia forms the haloalkene compound A, which causes nephrotoxicity in experimental animals. Numerous studies have shown no effects on postoperative renal function after moderate (1-3 hours) low flow sevoflurane, anesthesia. However, effects of longer exposures remain unresolved. The purpose of this study was to reveal the effects of low flow sevoflurane anesthesia in humans, following long duration surgery, on renal and hepatic functions compared to pre operation reading.

The study was carried out on 20 adult patients classified ASA I and II and of both sexes.

Pre and postoperative laboratory investigations were done for all patients before anesthesia and every day postoperatively for tow postopertive days. These included blood urea nitrogen, serum creatinine, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, serum total bilirubin and 24 hours urinary proteins, albumin, glucose and creatinine. The current study showed no significant differences in liver and renal function before and after long surgery with low flow sevoflurane.

DEDICATION

TO MY

DEAR FAMILY

ACKNOWLEDGEMENT

It is a great pleasure to express my sincere gratitude to my supervisor **Professor. Abdalla M Jarari,** for his guidance and encouragements and continuous support throughout the project to complete the study.

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ABBREVIATIONS

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APL	Adjustable pressure limiting
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
B	Bag
BUN	Blood urea nitrogen
BW	Body weight
CBC	complete blood count
C_S	Clearance substance
ECG	electrocardiogram
$ETCO_2$	End-tidal carbon dioxide
F^-	Fluoride ions
F_A	Alveolar concentrations
Fio_2	Inspired oxygen concentration
FGF	Fresh gas flow
GFR	Glomerular filtration rate
HFIP	Hexafluoroisopropanol
I.V	Intravenous
Kg	Kilograms
LDH	Lactate dehydrogenase
LFT_S	liver function tests
MAC	minimum alveolar concentration
PP mh	parts per million-hour
P_S	Plasma concentration of the substance
Sao_2	Oxygen saturation
SD	Standard deviation
T	Time elapsed in minutes
US	Urinary concentration of the substance
VNO_2	Nitrous oxide uptake in ml/min
V	Volumetric flow
VO_2	oxygen consumption

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Chapter 1

INTRODUCTION

1.1. SEVOFLURANE

Since the clinical introduction of holothane (in 1956) as the first nonflammable anesthetic agent (1,2), the quest for new inhalation anesthetic agents with better physical, pharmacokinetic and pharmacodynamic properties has centred upon the development of compounds with the following main properties (3,4),

Rapid and tolerable induction of, and recovery from anesthesia.

Rapid adjustment of the depth of anesthesia.

Adequate skeletal muscle relaxation.

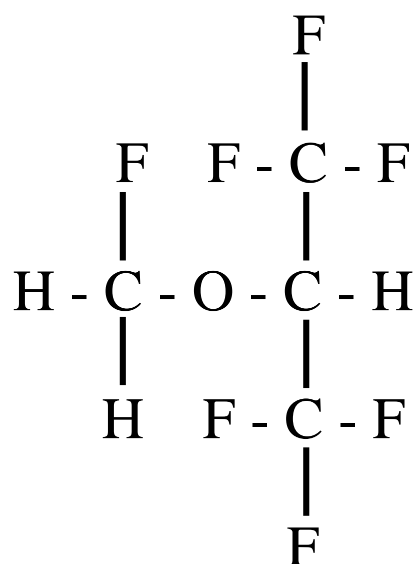
Wide safety margin between concentrations producing the desired pharmacological effect and those producing toxicity.

less of toxic effects or other adverse events at normal doses.

NAME OF THE DRUG:

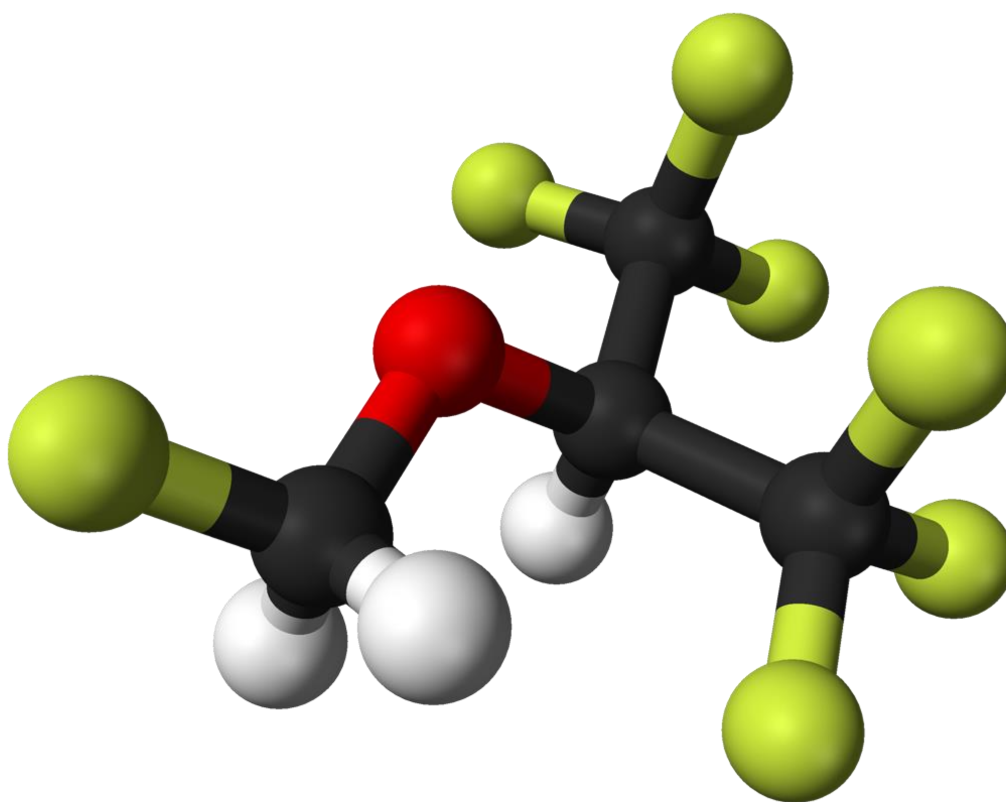
Non-proprietary name: fluoromethyl 2,2,2,-trifluoro-1-(trifluoromethyl) ethyl ether

Chemical structure:



Adopted from : http://quod.lib.umich.edu/m/medchem1ic/x-1191/sevoflurane___tif

Figure 1.1 : Structural formula of Sevoflurane



Adopted from: https://en.wikipedia.org/wiki/Sevoflurane

Figure 1.2: Ball-and-stick model of the sevoflurane molecule

Description:

Sevoflurane ($C_4H_3F_7O$), volatile liquid for inhalation, a non-flammable and nonexplosive liquid administered by vaporization, is a halogenated general inhalation anaesthetic drug.

Sevoflurane, Physical Constants are:

Molecular weight	200.05
Boiling point at 760 mm Hg	58.6°C
Specific gravity at 20°C	1.520 -1.525
Vapour pressure in mm Hg	157 mm Hg at 20°C
	197 mm Hg at 25°C
	317 mm Hg at 36°C

Sevoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Sevoflurane is non pungent. It is miscible with ethanol, ether, chloroform and petroleum benzene, and it is slightly soluble in water. It is stable when stored under normal room lighting conditions according to instructions. Sevoflurane is chemically stable. No discernible degradation occurs in the presence of strong acids or heat (5).

1.2. PHARMACOLOGY:-

1.2.1. Pharmacokinetics:

The wash-out of an anesthetic agent is influenced by its solubility in blood (as is the uptake), and agents with low blood solubility are likely to wash-out quickly from body tissues (6).

The low solubility of sevoflurane in blood would suggest that alveolar concentrations should rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent (7).

The rapid pulmonary elimination of sevoflurane minimizes the amount of anaesthetic available for metabolism. In humans, approximately 5% of absorbed sevoflurane is metabolized by CYP2 E1 to hexafluoroisopropanol (HFIP), with release of inorganic fluoride and CO_2 (or a one carbon fragment). Once formed, HFIP is rapidly conjugated with glucuronic acid and eliminated. No other metabolic pathways for sevoflurane have been identified. It is the only fluorinated volatile anaesthetic that is not metabolized to trifluoracetic acid (7).

Pharmacokinetics of fluoride Ion

Hepatic degradation of sevoflurane liberates inorganic fluoride ions (F^-) and the principal organic by-product hexafluoroisopropanol (HFIP) which accounts for 82% of the organic fluorinated metabolites (8). In humans, HFIP undergoes glucuronidation immediately after formation (9).

and the glucuronide conjugate is then primarily excreted in the urine (9,10). Peak urinary excretion of HFIP glucuronide, which has an excretion half-life of 55 hours (11), occurs in the first 12 hours after discontinuation of sevoflurane anesthesia (11,12), and little or none of

this metabolite is present in the plasma beyond 2 to 6 days after anesthesia (9,11).

Renal toxicity has not been reported even though fluoride is a metabolic product. Sevoflurane breaks down in the presence of soda lime, producing compound A fluoromethyl-2,2- difluoro-1-(trifluoromethyl) and giving rise to controversy and investigation although the toxicity of compound A is more theoretical than real.

Fluoride ion concentrations are influenced by the duration of anesthesia, the concentration of sevoflurane administered, and the composition of the anaesthetic gas mixture. Compared with healthy individuals, the fluoride ion half-life was prolonged in patients with renal impairment, but not in the elderly (5).

Compound A:

Although data from controlled clinical studies at low flow rates are limited, findings taken from patient and animal studies suggest that there is a potential for renal injury, which is presumed due to Compound A. Animal and human studies demonstrate that sevoflurane administered for more than 2 MAC and at fresh gas flow rates of <2 L/min may be associated with proteinuria and glycosuria (5).

While a level of Compound A exposure at which clinical nephrotoxicity might be expected to occur has not been established, it is prudent to consider all of the factors leading to Compound A exposure in humans, especially duration of exposure, fresh gas flow rate, and concentration of sevoflurane. During sevoflurane anesthesia the clinician should adjust inspired concentration and fresh gas flow rate to minimize exposure to Compound A. To minimize exposure to Compound A, sevoflurane exposure should not exceed 2 MAC at flow rates

of 1 to < 2 L/min. Because of limited clinical experience with sevoflurane in low-flow systems, fresh gas flow rates below 2L/min in a circle absorber system are not recommended.

1.2.2. Pharmacodynamics:

The anesthetic potency of sevoflurane, quantified as the minimum alveolar concentration (MAC) that, at steady state, produces immobility in 50% of individuals exposed to a noxious stimulus (13), as with other volatile anesthetic agents (14,15), the MAC of sevoflurane decreases with increasing age or with concomitant use of nitrous oxide (N_2O) (16), or opioids (17).

The MAC-awake, defined as the minimum alveolar concentration suppressing appropriate responses to verbal command (18), ranges from 0.60 to 0.68 % for sevoflurane (19,20) and, like MAC, it decreases with increasing age (20,21). The duration of anesthesia affects neither the MAC (6). nor the MAC-awake (22).

Sevoflurane is an inhalation anaesthetic agent for use in induction and maintenance of general anesthesia. Administration has been associated with a smooth, rapid loss of consciousness during inhalation induction and a rapid recovery following discontinuation of anesthesia. Minimum alveolar concentration (MAC) of sevoflurane in oxygen for a 40 year old adult is 2.1%.

Induction is accomplished with a minimum of excitement or of signs of upper respiratory irritation, no evidence of excessive secretions within the tracheobronchial tree and no central nervous system stimulation. Changes in the depth of sevoflurane anesthesia rapidly follow changes in the inspired concentration.

Sevoflurane is the only ethereal anesthesia that does not trigger a reflex response or cause airway irritation during inhaled induction.

Sevoflurane seems to be the pediatric anesthetic of choice and it is also highly useful for anesthesia in ambulatory patients. Sevoflurane gives rise to hemodynamic stability, is not arrhythmogenic, and does not sensitize the myocardium to the effects of catecholamines. The effects on cerebral blood flow are minimal at low concentrations.

Risks associated with CO_2 Absorbents:

When in contact with alkaline CO_2 absorbents within the anaesthesia machine, sevoflurane can undergo degradation under certain conditions. Sevoflurane should not be used with desiccated CO_2 absorbents.

The exothermic reaction that occurs with sevoflurane and CO_2 absorbents is increased when the CO_2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO_2 absorbent. Rare cases of extreme heat, smoke and/or spontaneous fire in the anesthesia machine have been reported during sevoflurane use in conjunction with the use of desiccated CO_2 absorbent. When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced before administration of sevoflurane. Degradation and formation of degradation products (methanol, formaldehyde, carbon monoxide, and Compounds A, B, C, D, and E) are increased by desiccated CO_2 absorbents (especially potassium hydroxide–containing absorbents), by increasing absorbent temperature, and by increased sevoflurane concentration.

1.3. Renal Functions:

Because clinical experience in administering sevoflurane to patients with renal insufficiency (creatinine >1.5 mg/dL) is limited, its safety in these patients has not been established. Limited pharmacology data in these patients appear to suggest that the half-life of sevoflurane may be increased. The clinical significance is unknown at this time. Thus, sevoflurane should be used with caution in these patients and renal function should be monitored postoperatively.

Sevoflurane may be associated with glycosuria and proteinuria when used for long procedures at low flow rates.

1.4. Hepatic Functions:

Results of evaluations of laboratory parameters (e.g., ALT, AST, alkaline phosphatase, and total bilirubin, etc.), as well as investigator-reported incidence of adverse events relating to liver function, demonstrate that sevoflurane can be administered to patients with normal or mild-to-moderately impaired hepatic functions. However, patients with severe hepatic dysfunction were not investigated.

1.5. Soda lime:

Is a mixture of chemicals, used in granular form in closed breathing environments, such as general anaesthesia, submarines, rebreathers and recompression chambers, to remove carbon dioxide from breathing gases to prevent CO_2 retention and carbon dioxide poisoning (23).

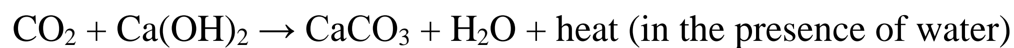
The main components of soda lime are:

- Calcium hydroxide, $Ca(OH)_2$ (about 75%)
- Water, H_2O (about 20%)

- Sodium hydroxide, NaOH (about 3%)
- Potassium hydroxide, KOH (about 1%).

While administering genearal anesthesia, the patient's expired gases, which contain carbon dioxide, are passed through an Anaesthetic machine breathing circuit filled with soda lime granules. Medical grade soda lime has indicating dye that changes color when the soda lime loses its carbon dioxide absorbing capacity.

The overall reaction is:



$CO_2 + Ca(OH)_2 \rightarrow CaCO_3 + H_2O$ + heat (in the presence of water)

The reaction can be considered as a strong base catalysed, water facilitated reaction (24).

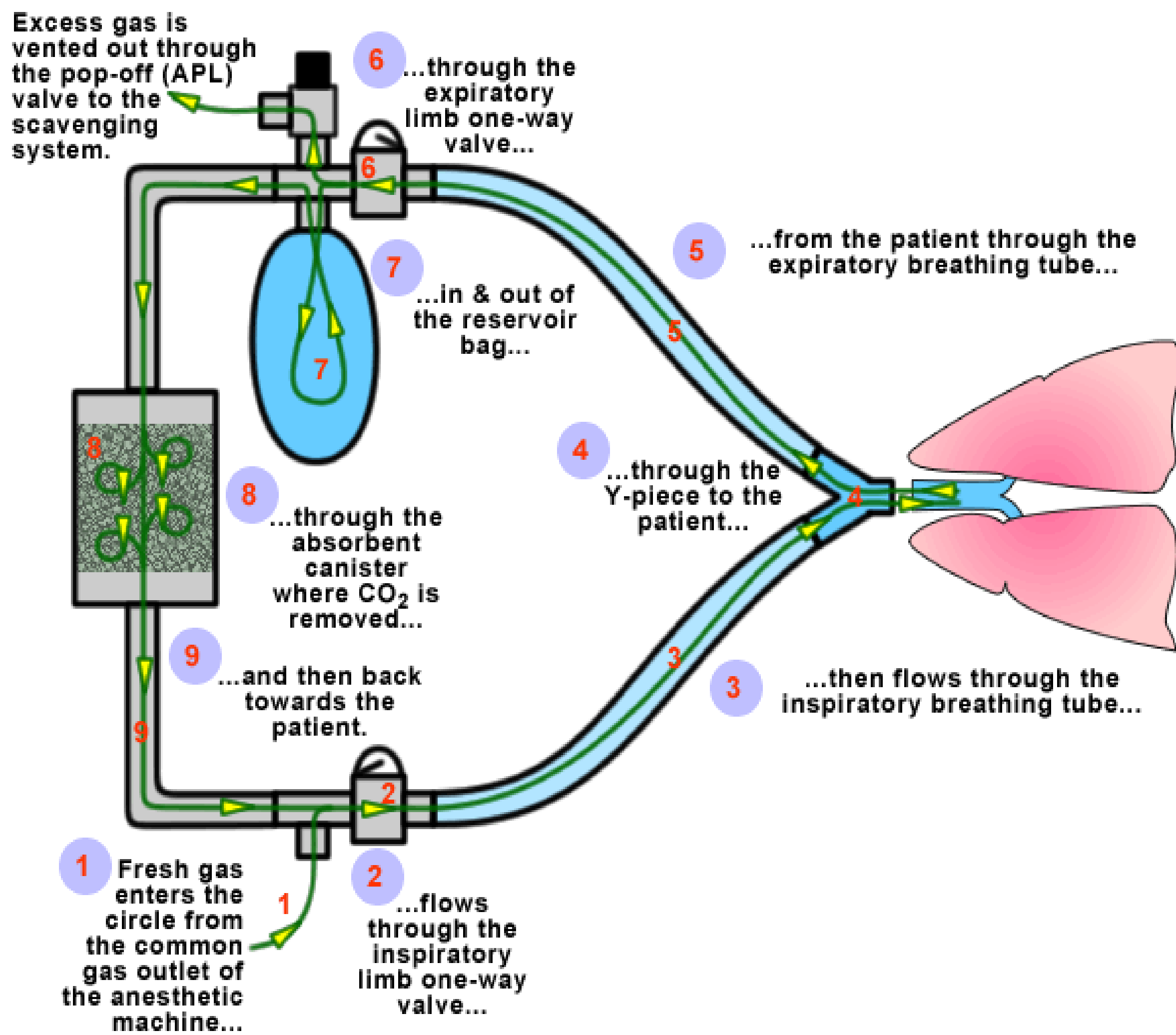
1.6. The Closed Circuit:-

A breathing system is defined as an assembly of components, which delivers gases from the anesthesia machine to the patients' airways. When the components are arranged as a circle, it is termed a circle system. The flow of exhaled gases is unidirectional in the system. The system contains a component (absorber), which absorbs exhaled carbon dioxide and it is not necessary to give high fresh gas flows as in Mapleson systems. When the adjustable pressure limiting (APL) valve is closed and all the exhaled gases without carbon dioxide are returned to the patient, the system becomes a totally closed one. Such a circle system can be used with flows as low as 250 to 500 mL and clinically can be termed as low-flow systems (25).

Low flow anesthesia can be defined as a technique which, using a rebreathing system, results in at least 50% of the exhaled air being

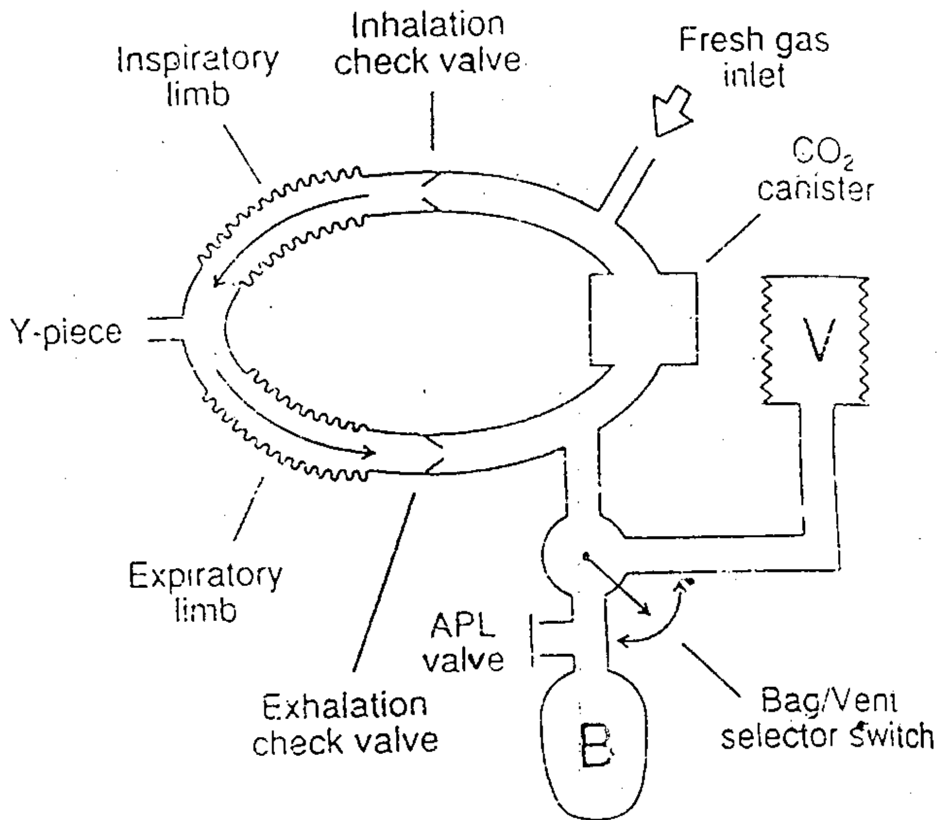
returned to the lungs after CO_2 absorption. If modern rebreathing systems are used, this degree of rebreathing is achieved only if the fresh gas flow is reduced to about 2L/min (26).

Closed system anesthesia is a term reserved for a technique in which significant leaks from the breathing system have been eliminated and maintenance fresh gas flow is just sufficient to replace the volume of gas and vapour taken up by the patient (27).



Adopted from: https://instruction.cvhs.okstate.edu/vmed5412/Lecture09.htm

Figure 1.3: The Circle System.



Adopted from: /http://slideplayer.com/slide/9334486

Figure 1.4 : Components of the circle system; B-Bag. V=Ventilator, APL=Adjustable pressure limiting.

1.7. Low flow anesthesia-the theory:

Rebreathing systems can be used in different ways:

If used with a fresh gas flow equal to the minute volume of the patient, the share of rebreathing will be negligible. Nearly completely, the expired air will be vented out of the system as excess gas via the adjustable pressure limiting valve (APL-valve), the patient gets nearly pure fresh gas (28).

If a flow of 4.0 L/min. is used, the share of rebreathing will increase to about 20%. The patient inhales a gas the composition of which is still resembling that of the fresh gas (28).

Only if the flow is reduced to 2.0 L/min. or lower values, the share of rebreathing will reach 50% or more. Thus, only when low fresh gas flows are used the share of rebreathing will become significant, and judicious use is made from the rebreathing technique(28).

According to the literature two different low flow techniques can be distinguished. The term low flow anesthesia was introduced by Foldes, starting an anesthetic technique performed with a fresh gas flow of 1.0 L/min (29). , Virtue introduced the term Minimal Flow Anesthesia by recommending the use of an even lower flow of 0.5 L/min (30).

As emphasized beforehand, the lower the fresh gas flow the lower is the amount of gas vented out of the breathing system as waste and the higher is the proportion of rebreathing.

The general term-low flow anesthesia-should be restricted to defining an anesthetic technique in which a semiclosed rebreathing system is used recirculating at least 50% of the exhaled air back to the

patient after CO_2 absorption .Using modern rebreathing systems this will be achieved only if the fresh gas flow is reduced to 2 L/min or less (26).

However, there is a limit for reducing the fresh gas flow. To prevent gas volume deficiency, at least the gas volume definitely taken up by the patient has to be delivered into the breathing system.

During the course of anesthesia, oxygen is taken up constantly by the patient in the range of the basal metabolic needs. It can be calculated by applying a simplified version of Brody's formula (31).

$VO_2 = 10 \times BW[Kg]^{3/4}$

Where VO_2 = oxygen consumption,

BW = Body weight,

Kg = Kilograms.

The uptake of nitrous oxide and the volatile anesthetic, however, follow a power function. Nitrous oxide uptake of a normal body weight adult patient can be roughly estimated by applying Severinghaus' formula (32).

$VN2O = 1000 \times t^{-1/2}$

Where VN2O = Nitrous oxide uptake in ml/min.

t = Time elapsed in minutes.

1.7.1. Characteristics of low flow anesthesia:

a- The lower the fresh gas flow, the greater the difference between the gas composition within the breathing circuit and the composition of the fresh gas. This may increase the risk of inadvertent hypoxia.

b- The lower the fresh gas flow, the longer the time constants for equilibration. This is a measure of the time it takes for alteration of the fresh gas composition to lead to corresponding alteration of the gas composition within the breathing system. Together with the previous character low flow may increase the risk of accidental misdosage of anesthetic agent.

c- The lower the fresh gas flow, the lower is the washout of exhaled g ases. This is due to reduction of the excess gas volume vented out of the system which may lead to accumulation of trace gases that might be harmful to the patients (33).

1.7.2. Advantages of low or minimal flow anesthesia:-

(A) Economic:

One of the principal advantages of low flow anesthesia is the enormous decrease that can be achieved in anesthetic gas consumption which in turn leads to considerable cost saving (26).

(B) Environmental:

Although there is no evidence that subanesthetic concentrations of anesthetic gases in the environment have significant harmful influences on the staff in the operating theatre, anesthetists must accept that increasingly stringent official regulations are being imposed concerning the maximum acceptable workplace concentrations of all anesthetic gases (34).

The extremely low anesthetic gas concentration levels acceptable in the operating room atmosphere can be achieved (even with careful maintenance of anesthetic apparatus and good attention to leaks from breathing systems) only by the use of low flow techniques (30), low flow

anesthesia reduces the exposure of the operating room personnel to inhalational anesthetics (35).

However, high flow anesthesia will inevitably result in pollution of the atmosphere beyond the operating theatre (36), occupational exposure to waste anesthetic gases has many deleterious effects on anesthetists and other operating room personnel (37).

Conservation of heat and humidity:

Inspiration of cool dry gases leads to impaired mucociliary function with subsequent microatelectasis, potential for infection and impaired gas exchange. Respiratory fluid loss and heat loss contribute to postoperative hypothermia after prolonged anesthesia, but use of appropriate gas flow rates can improve inspired gas humidification and temperature (38).

A raised temperature and water vapor content of the inhaled anesthetic gases preserve the anatomical and functional integrity of the ciliated epithelium of the respiratory tract (28). Low flow anesthesia significantly increases the warmth and humidity of anesthetic gases (39). The use of low fresh gas flow rate in patients provides relative humidity equivalent to circuit humidifiers (40).

1.7.3. Risks of low flow anesthesia:

(A) Increased risk of hypoxia:

During low flow anesthesia, if inhaling a mixture of oxygen together with other gases, there may be considerable differences between the inspired oxygen concentration and the oxygen concentration in the fresh gas. The lower the fresh gas flow and the higher the proportion of rebreathing, the lower the potential inspired concentration (assuming a

constant fresh-gas oxygen concentration). Thus to ensure that the potential inspired oxygen concentration remaining at a safe value, the oxygen concentration in the fresh gas must be increased as fresh gas flow decreases. Compliance with this simple rule is a safe way to avoid the delivery of hypoxic mixture during low flow anesthesia (26).

(B) Increased risk of over or under dosage of inhalation anesthetic:

In rebreathing circuits, it is necessary to deliver to the breathing circuits a total quantity of anesthetic agents that will maintain the alveolar concentration at the desired level while allowing the uptake by the body. During the early period of anesthesia this can not be achieved using low fresh gas flow. For this reason together with the need to allow nitrogen washed out from the body stores to be eliminated from the breathing system, it is necessary to use fresh gas flow of at least 3-4 L/min. for the first 15-20min. of anesthesia. Modern vaporizers feature flow compensation that guarantees the accurate delivery of the dialed concentration even at very low fresh gas flows (26).

Lower solubility should enable more rapid uptake and so potentially enables the flow to be reduced earlier (41). Also lower solubility implies less ongoing uptake of the anesthetic agent and so less risk of the alveolar concentrations decreasing progressively at the low flow rates. If the uptake of agent continues to be high, there is a risk that the alveolar concentration of the volatile agent will diminish and result in a change in the depth of anesthesia (42).

(C) Increased risk of hypercarbia:

The utilization period of carbon dioxide absorbent depends predominantly on the degree of rebreathing and the volume of the absorbent canister (43). Continuous carbon dioxide monitoring is a means by which the risk of accidental carbon dioxide rebreathing may be detected, as exhaustion of the absorbent can be recognized rapidly by an increase in the inspired concentration above zero (44).

(D) Increased risk of accumulation of dangerous trace gases:

During closed system and very low-flow anesthesia, there is a potential for accumulation of trace gases because of the low rate of washout as nitrogen ,methane and acetone (45).

(E) Nephrotoxic degradation products:

sevoflurane is degraded to produce compound A, especially with high minute ventilation, lower fresh gas flow, higher absorbent temperature, baralyme>sodalime, increasing anesthetic concentration and possibly increased carbon dioxide absorption (46).

1.7.4. Requirements for the safe use of low flow anesthesia:

(I) Oxygen saturation (SaO_2), end-tidal carbon dioxide ($ETco_2$) and inspired oxygen concentration (FiO_2) monitoring.

(II) Agent specific monitoring.

(III) A measure of circuit volume.

(IV) Presence of a leak–free circle system and CO_2 absorbent.

(V) Accurate flow meters (calibrated down to 0.2 L/min).

(VI) An inhalation anesthetic with very low solubility.

(VII) A delivery system, flow compensated to fresh gas flow (FGF) rates as low as 0.2 L/min.

(VIII) The following important considerations must be addressed when using low and minimal flow anesthesia:-

1- The delivered N_2O concentration should be reduced at flow rates below 0.5 L/min.

2- More frequent replacement of carbon dioxide absorbent canisters may be needed.

3- The need to washout the circuit occasionally during very long procedures.

4- The use of higher fresh gas flow rates initially to achieve anesthetic wash-in, and reach the desired inhaled concentrations rapidly (47).

1.8. Laboratory assessment of liver functions:

Because the liver performs multiple functions, no single laboratory test or battery of tests is sufficient to provide a complete estimate of the function of the liver in every clinical situation. A broad array of biochemical tests are used to assess many functions of the liver and to evaluate patients with suspected or established liver disease. These tests are referred to collectively as “liver function tests” (LFTs). This term has been criticized because the tests used most commonly to evaluate liver disease-the serum aminotransferase and alkaline phosphatase levels do

not actually assess a known systemic function of the liver but represent markers of liver cell damage or dysfunction (49).

- ***Aminotransferases:***

The aminotransferases- aspartate aminotransferase (AST), formerly serum glutamic oxaloacetic transaminase and alanine aminotransferase (ALT), formerly serum glutamic pyruvic transaminase are the most frequently used indicators of hepatic injury and represent markers of hepatocellular necrosis. These enzymes catalyze the transfer of the alpha-amino groups of aspartate and alanine to the alpha-keto group of ketoglutaric acid, resulting in the formation of oxaloacetic acid and pyruvic acid, respectively. These enzymes play a role in gluconeogenesis by facilitating the synthesis of glucose from non carbohydrate sources. AST is present in both the mitochondria (80 percent of the total) and cytosol (20 percent) of hepatocytes, but ALT is found only in the cytosol (50).

Numerous methods for assaying AST and ALT have been developed, and the normal range varies widely among laboratories. It is recommended to that the normal range be adjusted for sex and body mass index (51).

Serum levels of AST and ALT are elevated to some extent in almost all liver diseases. The highest elevations occur in severe viral hepatitis; drug or toxin induced hepatic necrosis, and circulatory shock (ischemic hepatitis (52). Determinations of serum aminotransferase have proved useful as screening tests for subclinical liver disease in asymptomatic persons (53).

- ***Alkaline phosphatase:***

Alkaline phosphatase is a family of isoenzymes that catalyze the hydrolysis of a number of phosphate esters at an alkaline pH. All enzymes in the family are glycoproteins that require zinc for activity.

Alkaline phosphatases are coded for by four genes: (54)

- One gene is known to code for alkaline phosphatase isoenzymes from liver, bone, first trimester placenta, and kidney (tissue-unspecific alkaline phosphatase).
- A second gene codes for alkaline phosphatase from third trimester placenta and intestine.
- A third gene codes for a second intestinal alkaline phosphatase.
- A fourth gene probably codes for fetal intestinal alkaline phosphatase.

In the human body alkaline phosphatase has been identified in liver, bone, intestine, placenta, kidney and leukocytes (55). Alkaline phosphatase detectable in serum, urine, bile, and lymph is thought to represent enzyme liberated from tissues.

In healthy people most circulating alkaline phosphatase originates from liver or bone.

In patients with an elevated level of serum alkaline phosphatase, the source is the liver in a majority of cases; but in up to one third of such individuals, no evidence of liver disease can be found. Bone disease characterized by increased osteoblastic activity also may be the source of an elevated serum alkaline phosphatase level, as may pregnancy. Only rarely is the intestine or kidney the source of an elevated serum level of alkaline phosphatase (56).

The highest elevations of serum alkaline phosphatase in patients with liver disease occur in cholestatic disorders. Elevations occur as a result of both intrahepatic and extra hepatic obstruction of bile flow, and the degree of elevation does not help to distinguish the two.

- ***Lactate dehydrogenase (LDH):***

Lactate dehydrogenase (LDH) is often included in liver biochemistry panels but has poor diagnostic specificity for liver disease.

Even measurement of LDH isoenzymes (i.e., LDH-5) has limited clinical usefulness (49).

- **Bilirubin:**

Bilirubin is an endogenous organic anion derived primarily from the degradation of hemoglobin released from aging red blood cells. Hemeoxygenase first breaks down hemoglobin into biliverdin, carbon monoxide, and iron. Biliverdin reductase then convents the former into bilirubin. Bilirubin is then released into blood, where it readily binds albumin. Inside hepatocytes bilirubin is conjugated (primarily with glucuronide) and actively excreted into bile canaliculi. Jaundice is usually clinically obvious when total bilirubin exceeds 3 mg/dl. A predominantly conjugated hyperbilirubinemia may reflect hepatocellular dysfunction, intrahepatic cholestasis, or extrahepatic biliary obstruction. Hyperbilirubinemia that is chiefly unconjugated may be seen with hemolysis or with congenital or acquired defects in bilirubin conjugation (49).

1.9. Laboratory assessment of renal functions:

- ***Urea:****-*

Urea is the major nitrogen containing metabolic product of protein catabolism in humans, accounting for more than 75% of the nonprotein nitrogen eventually excreted.

Measurement of the plasma or serum urea concentration is widely regarded as a test of renal function. However, a number of non renal factors influence the circulating urea concentration and consequently limit its utility as a test of renal function. For example, urea production and consequently urea concentration are increased by a high protein diet, increased protein catabolism, muscle wasting (as in starvation), reabsorption of blood proteins after a gastrointestinal hemorrhage, treatment with cortisol or its synthetic analogues, in some cases of chronic liver disease, and with decreased perfusion of the kidneys.

The plasma urea will also depend on the state of hydration of the patient. In all the above pre-renal situations, the plasma creatinine concentration will be normal. In postrenal conditions where obstruction to the flow of urine is present (e.g., malignancy, nephrolithiasis, and prostatism), both the plasma creatinine and urea levels will be increased (57).

Although blood urea nitrogen (BUN) continues to be used for ordering the plasma or serum urea nitrogen test, this terminology is incorrect, as blood is rarely analyzed for urea. The factor 2.14 is used for converting urea nitrogen mass units to those of urea.

- ***Creatinine:-***

Creatinine is synthesized in the kidneys, liver and pancreas. Because creatinine is endogenously produced and released into body fluids at a constant rate and its plasma levels are maintained within narrow limits, its clearance can be measured as an indicator of glomerular filtration rate (GFR) (58).

The serum creatinine level is determined by creatinine production, state of hydration, and creatinine excretion. Increased creatinine production is seen in acute muscle disease such as dermatomyositis, and decreased creatinine production is seen in muscle-wasting diseases. Decreased renal perfusion, as in shock, hypotension, congestive heart failure, or cirrhosis, will decrease the GFR and raise serum creatinine.

Calculating the serum urea nitrogen : creatinine ratio may be of benefit in separating prerenal and postrenal conditions from renal diseases as a cause of an elevated serum creatinine or urea level. The normal serum urea nitrogen : creatinine ratio is in the range of 10 : 1 to 20 : 1, it is elevated in prerenal and postrenal conditions and is in the normal range in renal disease.

A number of methods are used to measure the GFR. Most involve the kidneys ability to clear either an exogenous or endogenous marker.

The renal clearance of a substance is defined as the volume of plasma from which the substance is completely cleared by the kidneys per unit time (59).

The clearance of a substance is given by:

$$Cs = \frac{Us\ XV}{Ps}$$

Where: **Cs** = Clearance in units of milliliters of plasma cleared of a substance per minute.

Us = Urinary concentration of the substance.

V = Volumetric flow rate of urine in milliliters per minute .

Ps = Plasma concentration of the substance.

The marker used for measurement of GFR should be:

(1) Freely filterable at the glomerular barrier, (2) not reabsorbed by the tubules, (3) not secreted by the tubules, (4) present at a stable plasma concentration.

Creatinine: is the most widely used endogenous marker of GFR is measurement of serum creatinine and urine creatinine.

- ***Urinary albumin:-***

Glomerular integrity can be assessed by measuring the concentration of urine protein (either total and/or individual proteins) that is predominantly retained by the healthy glomerulus (60).

If glomerular permeability increases as a consequence of inflammation or basement membrane damage, there will be an increase in the filtered load of all proteins. The most characteristic feature, however, will be the increasing amounts of the higher molecular weight proteins such as albumin excreted into the urine (60).

1.10. Aim of this study:

The aim of this study is to evaluate the effects of low flow sevoflurane anesthesia on hepatic and renal functions in lengthy surgical operation.

Chapter 2

PATIENTS AND METHODS

2.1. Patient eligibility:

After approval of departmental ethics and research committee and obtaining informed consent, Twenty adult patients of American Society of Anesthesiologists (ASA) physical status class I or II were randomly allocated as one group (n =20).

Choice of patients:-

The patients were scheduled for surgery of suspected duration > 4 hours at Tobruk Medical center. Their choice obeyed the following criteria:

Inclusion Criteria:

- Sex: Male and Female
- Age: 18-55 years old.
- ASA class: I and II.

Exclusion Criteria:

Any of the following would be a criterion for exclusion.

- Age < 18 or > 55 years.
- Diabetic and obese patients.
- Patients with history of receiving anti-psychotic drugs or alcohol.
- Patients with history, clinical or laboratory findings of hepatic, renal, cardiovascular or pulmonary disease.
- Patients with personal or family history of malignant hyperthermia.
- Patients scheduled for urologic or hepatobiliary surgery.

2.2. Anesthetic management :

A standard technique of anesthesia was used for all patients.

A) Preoperative preparation:

- Complete medical history was taken from each patient.
- All patients were physically examined preoperatively to assess their degree of fitness for both surgery and anesthesia and to assess their ASA physical status.
- 10 ml blood sample and 24 hours urine were collected from each patient preoperatively for base line laboratory evaluation, the following parameters were measured.

(a) Blood investigations:

- Aspartate aminotransferase (AST).
- Alanine aminotransferase (ALT).
- Alkaline phosphatase (ALP).
- Lactate dehydrogenase (LDH).
- Total bilirubin.
- Blood urea nitrogen (BUN).
- Serum creatinine.

(b) Urine analysis for:

- 24 hours urine albumin.
- 24 hours urine glucose.
- 24 hours urine creatinine.

- Other routine preoperative investigations like fasting and post prandial blood sugar, complete blood count (CBC), and electrocardiogram (ECG) were done.

Pre anesthetic medication:

A 20 gauge canula was inserted in a peripheral vein. All patients were premedicated by intravenous (i.v) midazolam 1mg immediately before induction.

(C) Pre induction

- Prior to induction, an intravenous infusion started and the patient received at least 0.5 ml/kg Ringer lactate each hour interval while the patient was fasting.
- Standard sensors and monitors were connected to the patient, these included:

1- ECG.

2- Pulse oximetry.

3- Automated blood pressure cuff.

4- Capnography and anesthetic agent monitor showing both inspiratory and expiratory carbon dioxide and both inspiratory and expiratory concentration of anesthetic agent.

(D) Induction of anesthesia:

- Sodalime in the anesthetic machine was changed before each patient.
- Pre oxygenation for at least 3 minutes was allowed via face mask with 100% oxygen then anesthesia was induced by Fentanyl 1.5µg/kg i.v., Lidocaine 0.5-1.0 mg/kg i.v., Propofol 2-2.5 mg/kg i.v. and pancronium 0.04 to 0.08 mg/kg i.v. while the patients were

breathing pure oxygen. When proper muscle relaxation was achieved, the patients were intubated with oro-tracheal cuffed tube.The tube was secured and connected to the anesthetic machine. The chest was checked for equal air entry in both lungs.Capnography and anesthetic agent monitor were connected to the patients.

(E) Maintenance of anesthesia:

Following induction of anesthesia lungs were mechanically ventilated initially with a tidal volume of 7 to 10 ml/kg, with a ventilatory rate of 12 breath/minute, then both tidal volume and respiratory rate were adjusted to maintain end-tidal CO_2 of 30-35 mmHg. Muscle relaxation was maintained with pancronium top up doses. Proper analgesia was maintained throughout the operation with Fentany1 i.v. bolus doses of 50 to 100 µg according to hypertensive response.

Delivery of inhalational anesthetics:

Upon connection to the anesthetic circuit, a fresh gas flow of 4L/min. of pure oxygen, for at least 20 minutes was delivered to allow for denitrogenation of the lungs and proper equilibrium between inspired and alveolar gas then the flow was reduced to a total flow of 1L/min of both oxygen and nitrous oxide for the rest of the procedure.

Patients were assigned to inhale 1.0 to 1.3 MAC of sevoflurane together with oxygen and nitrous oxide in a ratio adjusted to maintain the oxygen concentration in the inspiratory limb at more than 30%. The inhalational anesthetic concentrations were adjusted to maintain systolic blood pressure within 20% of baseline.

(F) Recovery from anesthesia:

At the end of surgery and after closure of skin the inhalational anesthetic was discontinued. Fresh gas flow was increased to 4-6 L/min of pure oxygen, neostigmine 0.05 mg/kg, and atropine 0.02 mg/kg were given intravenously for reversal of residual muscle relaxation.

Patients were extubated after recovery of the protective airway reflexes.

(G) Blood sampling and urine collection:

- Two samples of venous blood (10ml each) were taken at 1st and 3rd day after anesthesia for measurement of blood urea nitrogen, serum creatinine, aspartate aminotransferase (AST), alanine amino- transferase (ALT), Lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and total bilirubin.
- Twenty-four hours period urine in the 1st, and 3rd days after anesthesia was collected for measurement of 24 hours urine creatinine, glucose and albumin.

(H) Monitoring of inhalation anesthetic concentration using a pre-calibrated multigas analyzer (built-in the anesthesia machine). The alveolar concentrations (FA) of volatile anesthetics were recorded at 10min. intervals and calculating the mean of all readings for each patient and the total duration of surgery was recorded in each patient to calculate the MAC-hour exposure to inhalation anesthetic by divding the mean of all readings of (FA) by the (MAC) value of the inhalational anesthetic used and multiplying the result by the duration of anesthesia in hours.

2.3. Methods:

2.3.1. Blood collection

Venous blood samples were drawn from all the participants. Blood was collected in plain tubes, and sera were separated from plain tubes and stored until the assays were performed .

2.3.2. Urine collection:

The first voided morning specimen is particularly valuable because it is more concentrated and abnormalities are easier to detect. 24-hour urine specimen is put into a large collection bottle. To prevent breakdown of urinary components, the collection has a preservative added to it or is refrigerated. The laboratory needs at least 10 ml of urine for a routine UA.

2.3.3. Instruments:

The measurements of Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Lactate dehydrogenase (LDH), Total bilirubin, Blood urea nitrogen and Serum creatinine was measured using fully automated system (VITROS 2005,USA)

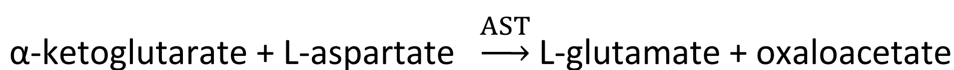
urine albumin, urine glucose and urine creatinine was measured using BIOTEC SCA 1000 (Germany).

2.3.4. Estimation of serum Aspartate aminotransferase (AST).

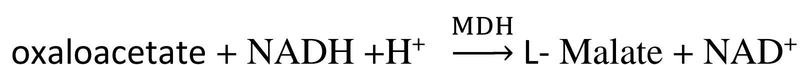
Test principle:

Enzymatic Kinetic Method:

AST catalyzes the transamination of L-aspartate to a-ketoglutarate forming L-glutamate and oxaloacetate. The oxaloacetate formed is reduced to malate by Malate dehydrogenase (MDH) with simultaneous oxidation of reduced NADH to NAD.



$$\alpha\text{-ketoglutarate} + \text{L-aspartate} \xrightarrow{AST} \text{L-glutamate} + \text{oxaloacetate}$$



$$\text{oxaloacetate} + \text{NADH} + H^+ \xrightarrow{MDH} \text{L- Malate} + NAD^+$$

The system monitors the rate of change in absorbance at 340 nanometers

Calculation:

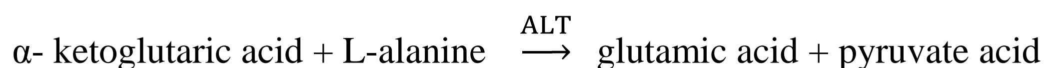
VITROS nalyzer automatically calculate the analyte concentration of each
sample.

2.3.5. Estimation of serum alanine aminotransferase (ALT).

Test principle:

Enzymatic Kinetic Method:

ALT catalyzes the transamination from L-alanine to a- ketoglutaric acid, forming L- glutamic acid and pyruvic acid, the pyruvate that is formed reacts with reduced NADH in the presence of lactate dehydrogenase to form lactic acid and oxidized NAD.



$$\alpha\text{- ketoglutaric acid} + \text{L-alanine} \xrightarrow{ALT} \text{glutamic acid} + \text{pyruvate acid}$$

The rate of conversion of the reduced cofactor to the cofactor can be determined by monitoring the decrease in absorbance bichromatically at 340 nanometers.

Calculation:

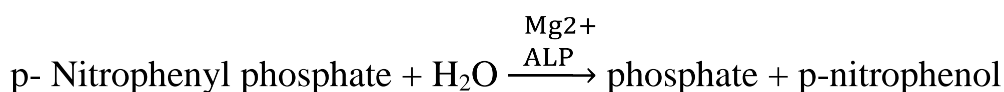
VITROS nalyzer automatically calculate the analyte concentration of each sample.

2.3.6. Estimation of serum alkaline phosphatase (ALP).

Test principle:

Enzymatic Kinetic Method**:**

Alkaline phosphatase in serum catalyzes the hydrolysis of colorless p-nitrophenyl phosphate to p-nitrophenol and inorganic phosphate**.**



$$\text{p- Nitrophenyl phosphate} + H_2O \xrightarrow[\text{ALP}]{\text{Mg2+}} \text{phosphate} + \text{p-nitrophenol}$$

In an alkaline solution, p-nitrophenol is in the phenoxide form and has a strong absorbance at 408 nm.

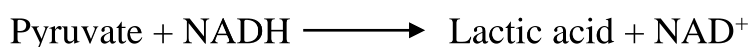
Calculation:

VITROS nalyzer automatically calculate the analyte concentration of each sample.

2.3.7. Estimation of serum Lactate dehydrogenase (LDH).
Test principle:

Enzymatic Kinetic Method**:**

The LDH method measures the oxidation of L-lactate to pyruvate with simultaneous reduction of nicotinamide adenine dinucleotide (NAD).



$$\text{Pyruvate} + \text{NADH} \longrightarrow \text{Lactic acid} + NAD^{+}$$

The change in absorbance at 340 nm due to the appearance of reduced NAD (NADH) is directly proportional to the LDH activity**.**

Calculation:

VITROS nalyzer automatically calculate the analyte concentration of each sample.

2.3.8. Estimation of serum total bilirubin.

Test principle:

colorimetric method:

Totel bilirubin reacts in acid medium withh diazotized sulfanilic acid to form a red colored azobilirubin,The intensity of color produced results is the directly proportional to the amount of bilirubin present in the sample.

Calculation:

VITROS nalyzer automatically calculate the analyte concentration of each sample.

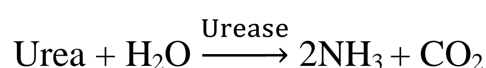
2.3.9. Estimation of Blood urea nitrogen (BUN).

Test principle:

Urease-colorimetric method:

The reaction involved in the assay system is as follows:

Urea is hydrolyzed in the presence of water and urease to produce ammonia and carbon dioxide.



$$\text{Urea} + H_2O \xrightarrow{\text{Urease}} 2NH_3 + CO_2$$

The free ammonia in an alkaline pH and in the presence of indicator forms coloured complex proportional to the urea concentration in the specimen.

Calculation:

VITROS nalyzer automatically calculate the analyte concentration of each sample.

Formulas: BUN (mg/dl) = Urea (mg/dl) / 2.1428

2.3.10. Estimation of serum creatinine.

Test principle:

colorimetric method:

Creatinine reacts with picric acid in alkaline conditions to form a yellow-orange color complex.

The rate of formation of color is proportional to the creatinine quantity in the sample.

Calculation:

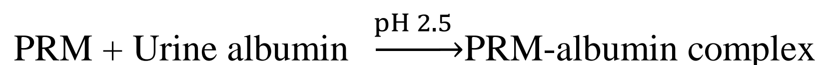
VITROS nalyzer automatically calculate the analyte concentration of each sample.

2.3.11. Estimation of 24 hours urinary albumin.

Test principle:

colorimetric method:

the method measures the shift in the absortion spectrum from 460 to 600 nm of the complex that occurs at acid pH between pyrogallool red-molibdate (PRM) and the basic amino group of urine albumin.



$$\text{PRM + Urine albumin} \xrightarrow{\text{pH 2.5}} \text{PRM-albumin complex}$$

Reagents:

R1: pyrogallol Reagent. succinate buffer 60 mmol/L pH 2.5, pyrogallol red 0.06 mmol/L, sodium molibdate 0.04 mmol/L, sodium dodecyl sulfate 0.08 mmol/L.

CAL:urine albumin standard. Albumin 200mg/dl. Buffered mixture (80/20) on an artificial matrix .

Procedures:

Tube	Blank	Sample	CAL.standard
R1	1.0ml	1.0 ml	1.0 ml
Sample	_	20 µl	_
CAL.standard	_	_	20 µl

Mix and incubate the tubes 5 minutes at 37 °C or 10 minutes at room temperature. Read the absorbance (A) of the samples and the standard at 600 nm against the reagent blank.

The color is stable for 30 minutes protected from light.

Calculation:

$$\frac{\text{A sample}}{\text{A standard}} \times \text{v} \times \mathbf{2000} = \text{mg/24} - \text{h}$$

V= Liters urine /24-h

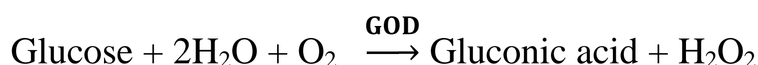
2000= mg/L standard

2.3.12. Estimation of 24 hours urinary glucose.

Test principle:

Enzymatic colorimetric method(GOD-POD) :

Glucose is determined after enzymatic oxidation in the presence of glucose oxidase. The formed hydrogen peroxide reacts under catalysis of peroxidase (PAP) with phenol and 4-aminoantipyrine to form a red violet quinoneimine dye asindicator.



Glucose + $2H_2O$ + O_2 $\xrightarrow{\text{GOD}}$ Gluconic acid + H_2O_2

$2H_2O_2$ + phenol + 4-amino-antipyrine $\xrightarrow{\text{PAP}}$ 4H2O + Quinoneimine

Reagents:

R1:glucose standard 5.56 mmol/L.

R2: phosphate Buffer 100 mmol/L, glucose oxidase 10000 U/L, peroxidase 2000 U/L, 4-amino-antipyrine 1mmol/L, Phenol 10mmol/L.

Procedures:

Dilute 24h-Urine 1:10 with physiologic solution

Tube	Blank	Standard	Sample
R2	1000 µl	1000 µl	1000 µl
Distilled water	10 µl	_	_
Standard	_	10 µl	_
Sample	_	_	10 µl

Mix, incubate for 10 min at 37 ºC and read sample and standard extinetion. Volumes can be proportionally modified.

Calculation:

$$\text{Glucose mg}/24\text{h} = \frac{\text{A sample}}{\text{A standard}} \times 10 \ \times \text{L}/24\text{h}$$

10 = dilution rate.

2.3.13. Estimation of 24 hours urinary creatinine.

Test principle:

colorimetric method:

Creatinine reacts with picric acid in alkaline conditions to form a yellow-orange color complex. The rate of formation of color is proportional to the creatinine quantity in the sample.

Reagents:

R1:creatinine standard 2.0 mg/dl

R2: picric acid 38mmol/l

R3:sodium hydroxide 0.4 mmol/l

Reagent preparation:

Mix reagents (R2) and(R3) in the ratio 1+1 = (Working reagent).

Working reagent is stable 2 days at room temperature.

Procedures:

Dilute 24h-Urine 1:50 with physiologic saline 0.9%.

Tube	Sample	Standard
Working reagent	1000µl	1000µl
Sample	100µl	–
CAL.standard	–	1000µl

Mix, and after 30 sec. read the absorbance A1of the standard or specimen. Exactly 2 min. later absorbance A2 of standard or specimen.

Calculation:

A2 - **A1** = A specimen or A standard.

$$\text{creatinine mg /dl} = \frac{\mathbf{A}\text{ specimen}}{\mathbf{A}\text{ standard}} \times 2 \times 50$$

50 = dilution rate**.**

2.4. STATISTICAL ANALYSIS

The data were analyzed using the statistical package for the social sciences (SPSS). Descriptive characteristics of the study calculated as mean ± standard deviation (SD). P-values < 0.05 were regarded as statistically significant. One way analysis of variance (ANOVA) was used.

Chapter 3

RESULTS

Table 3.1: Demographic characteristics of patients, duration of anesthesia and MAC-h exposure to inhalation anesthetic (mean ± SD).

patients	mean ± SD	P-value
Age (years)	42 ± 11	0.558
Sex (M/F)	14/16	0.438
Height (cm)	161 ± 12	0.166
Weight (Kg)	65 ± 15	0.134
Duration of anesthesia (min)	350 ± 45	0.150
MAC-h	10.2 ± 2.3	0.063

Table 3.2: Serum aspartate aminotransferase (AST) (IU/L) in preoperative day and 1st and 3rd days postoperative (data represent means ± SD).

*= Significance at p < 0.05

AST	Pre-operative	First day	Third day
Range	13.50 – 31.0	25.0 – 45.20	22.80 – 35.50
Mean ± SD	19.59 ± 4.047	32.20 ± 4.298	28.94 ± 3.499
F. test	54.564		
p. value	0.001		

Pre-operative & First day	Pre-operative & Third day	First day & Third day
0.001*	0.001*	0.012*

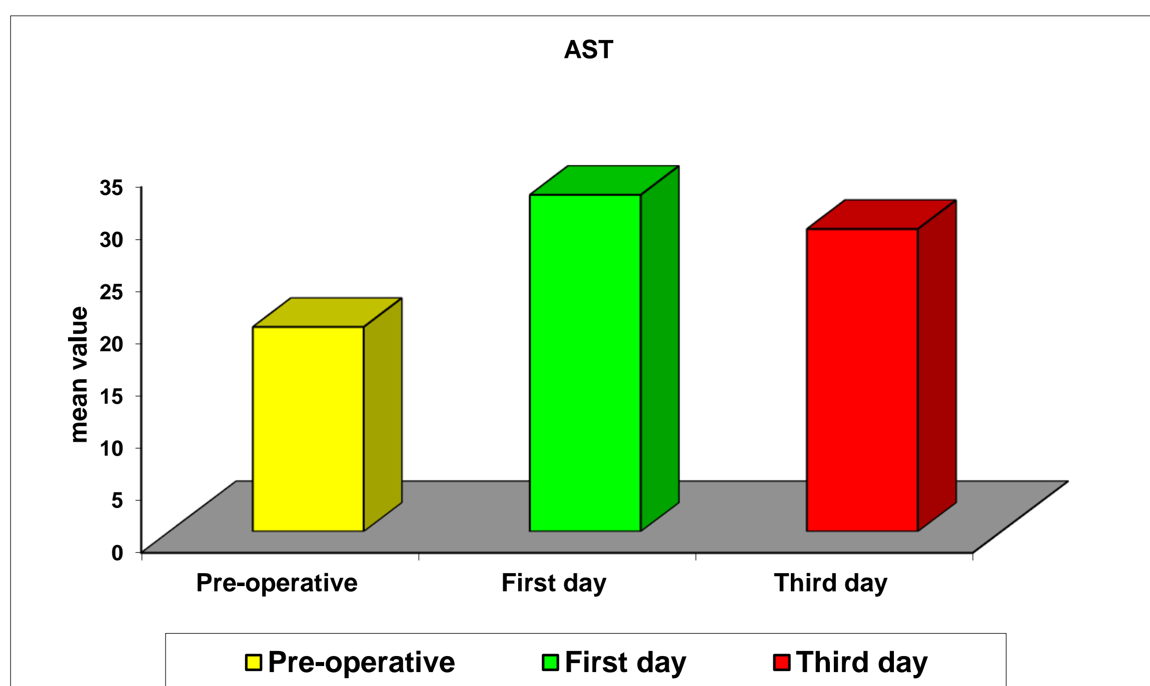


Figure 3.1: Serum aspartate aminotransferase (AST) (IU/L) in preoperative day and 1st and 3rd days postoperative.

Table 3.3: Serum alanine aminotransferase (ALT) (IU/L) in preoperative day and 1st and 3rd days postoperative (data represent means $\pm$ SD).

*= Significance at $p < 0.05$

ALT	Pre-operative	First day	Third day
Range	9.30 – 18.80	20.50 – 42.50	18.60 – 35.60
Mean $\pm$ SD	15.045 $\pm$ 1.925	29.01 $\pm$ 4.466	25.32 $\pm$ 4.411
F. test	72.887		
p. value	0.001		

Pre-operative & First day	Pre-operative & Third day	First day & Third day
0.001*	0.001*	0.003*

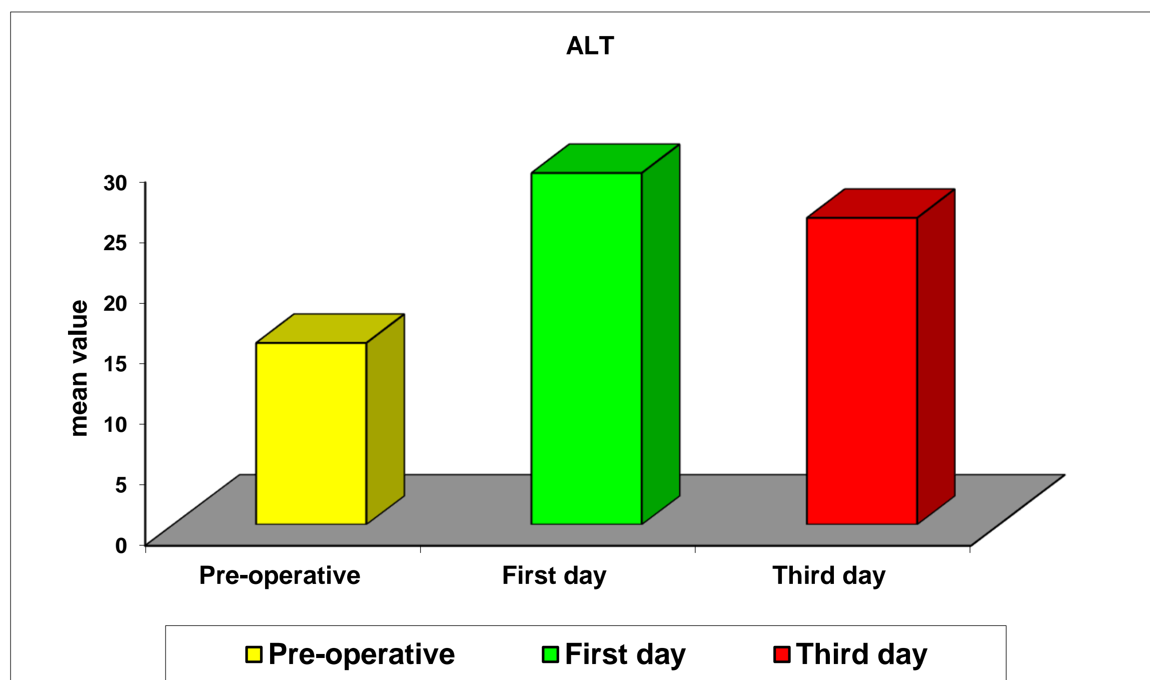


Figure 3.2: Serum alanine aminotransferase (ALT) (IU/L) in preoperative day and 1st and 3rd days postoperative

Table 3.4: Serum alkaline phosphatase (ALP) (IU/L) in preoperative day and 1st and 3rd days postoperative (data represent means ± SD).

*= Significance at $p < 0.05$

ALP	Pre-operative	First day	Third day
Range	78 – 305	65 – 266	72 – 272
Mean ± SD	160.8 ± 48.24	109.33 ± 42.47	123.47 ± 39.51
F. test	7.455		
p. value	0.001		

Pre-operative & First day	Pre-operative & Third day	First day & Third day
0.001*	0.009*	0.309

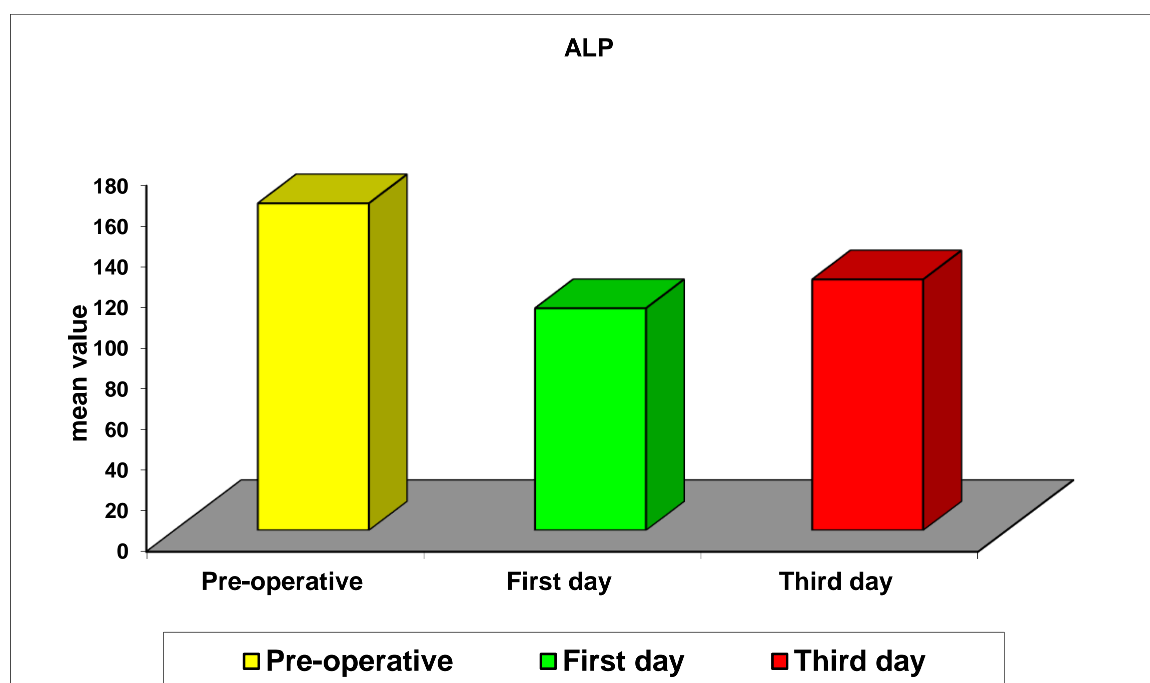


Figure 3.3: Serum alkaline phosphatase (ALP) (IU/L) in preoperative day and 1st and 3rd days postoperative.

Table 3.5: Serum lactate dehydrogenase (LDH) (IU/L) in preoperative day and 1st and 3rd days postoperative (data represent means ± SD).

*= Significance at $p < 0.05$

LDH	Pre-operative	First day	Third day
Range	197 – 575	178 – 460	145 – 350
Mean ± SD	362.8 ± 80.99	294.3 ± 75.69	238.0 ± 59.25
F. test	14.832		
p. value	0.001		
Pre-operative & First day	**Pre-operative & Third day**	**First day & Third day**	
0.004*	0.001*	0.017*	

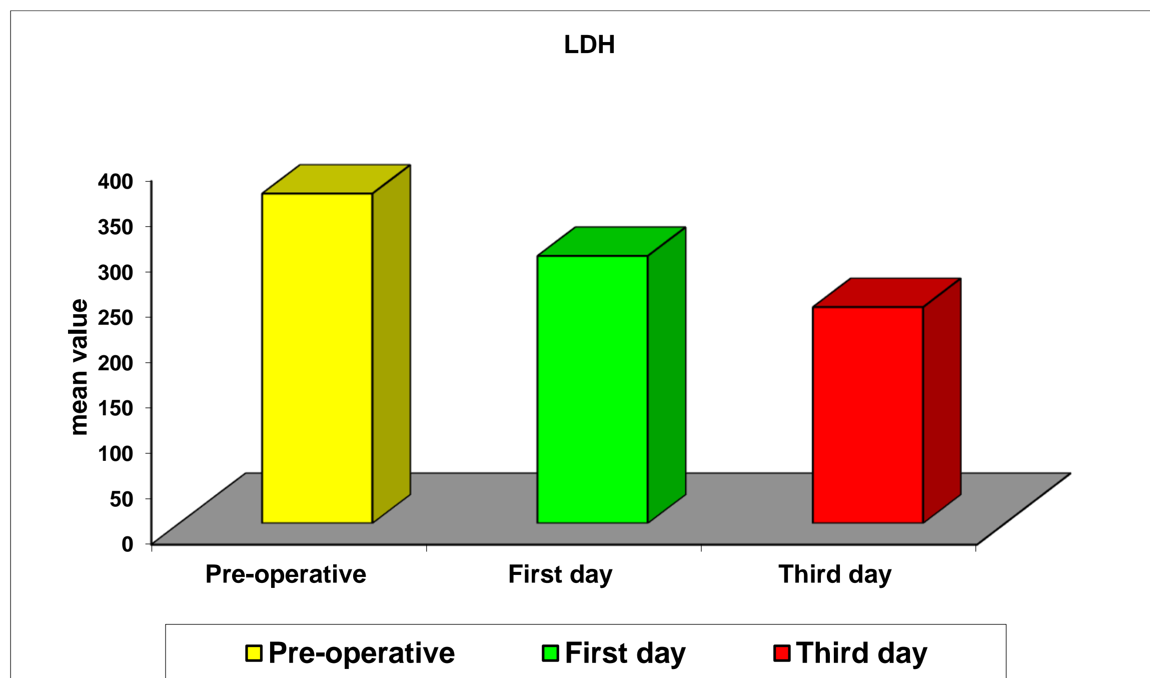


Figure 3.4: Serum lactate dehydrogenase (LDH) (IU/L) in preoperative day and 1st and 3rd days postoperative.

Table 3.6: Serum total bilirubin (mg/dl) in preoperative day and 1st and 3rd days postoperative (data represent means ± SD).

*= Significance at $p < 0.05$

Serum total bilirubin	Pre-operative	First day	Third day
Range	0.30 – 0.70	0.60 – 1.20	0.50 – 1.10
Mean ± SD	0.50 ± 0.103	0.805 ± 0.154	0.710± 0.137
F. test	27.562		
p. value	0.001		

Pre-operative & First day	Pre-operative & Third day	First day & Third day
0.001*	0.001*	0.028*

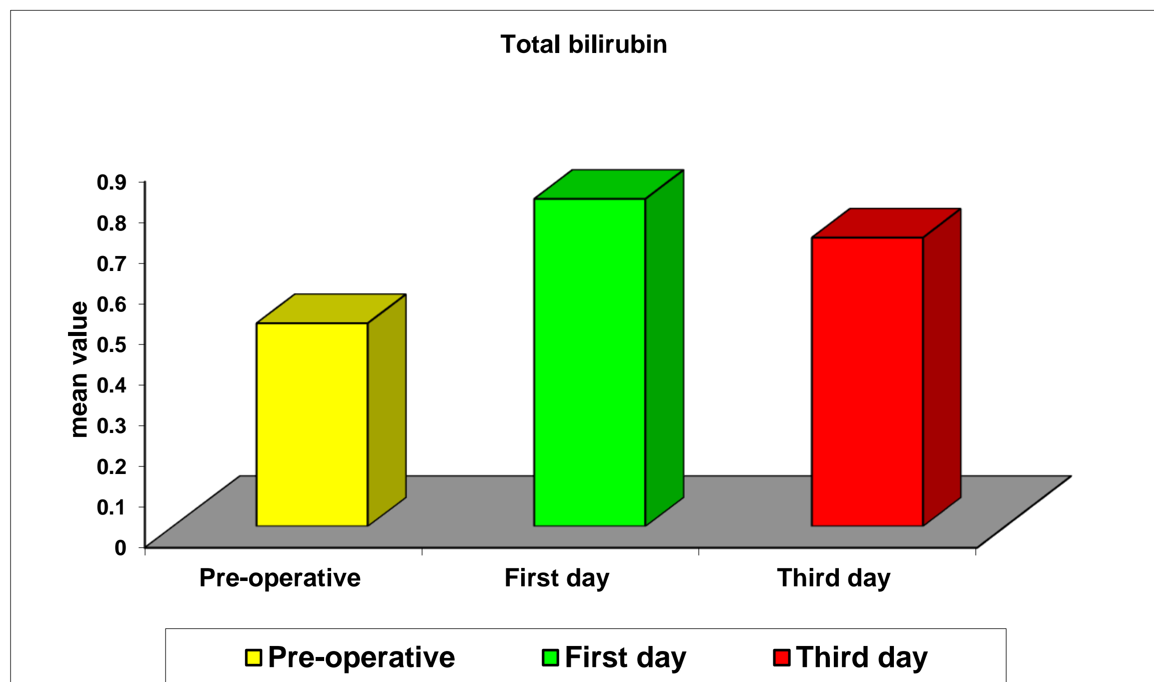


Figure 3.5: Serum total bilirubin (mg/dl) in preoperative day and 1st and 3rd days postoperative

Table 3.7: Blood urea nitrogen (BUN) (mg/dl) in preoperative day and 1st and 3rd days postoperative (data represent means ± SD).

*= Significance at $p < 0.05$

Urea nitrogen	Pre-operative	First day	Third day
Range	9.60 – 18.0	6.50 – 16.0	8.10 – 16.80
Mean ± SD	13.04 ± 1.86	9.53 ± 2.21	11.06 ± 1.96
F. test	15.180		
p. value	0.001		

Pre-operative & First day	Pre-operative & Third day	First day & Third day
0.001*	0.003*	0.020*

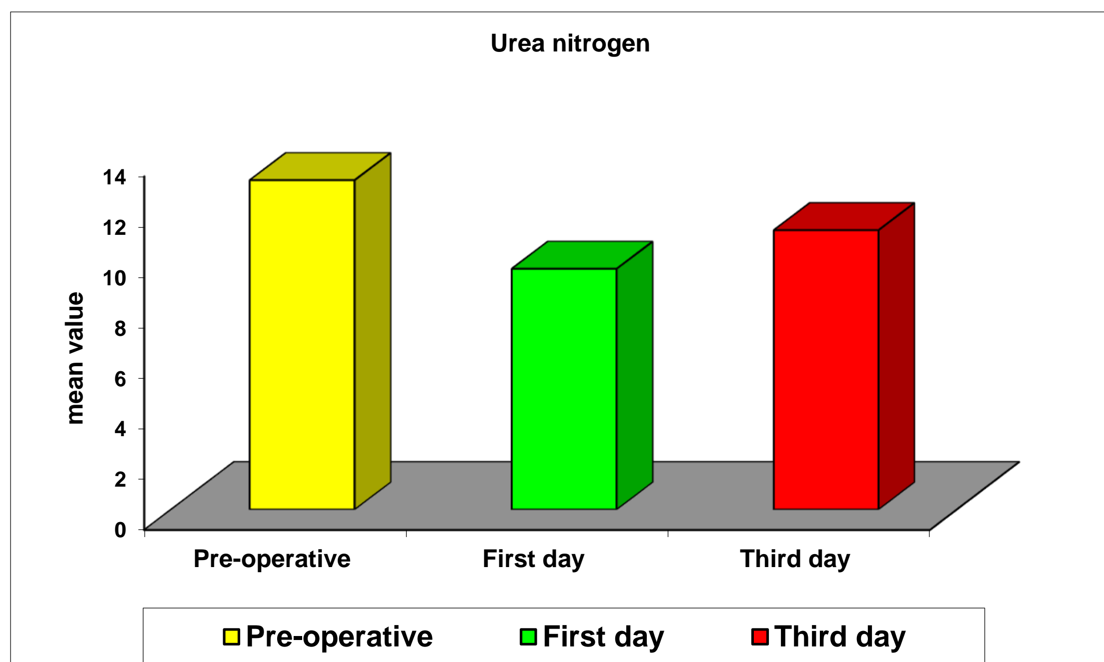


Figure 3.6: Blood urea nitrogen (BUN) (mg/dl) in preoperative day and 1st and 3rd days postoperative.

Table 3.8: Serum creatinine (mg/dl) in preoperative day and 1st and 3rd days postoperative (data represent means ± SD).

*= Significance at $p < 0.05$

Serum creatinine	Pre-operative		First day	Third day
Range	0.40 – 0.80		0.40 – 0.80	0.40 – 0.70
Mean ± SD	0.54 ± 0.118		0.54 ± 0.094	0.51 ± .093
F. test	0.395			
p. value	0.676			
Pre-operative & First day	Pre-operative & Third day		First day & Third day	
0.995	0.445		0.445	

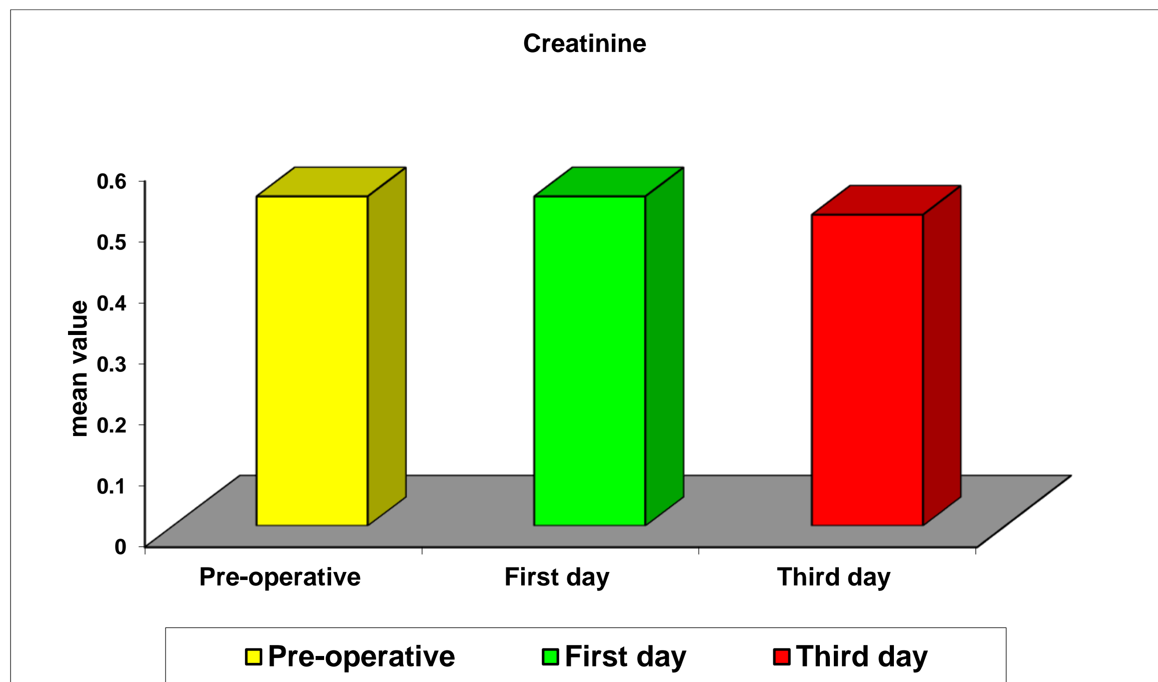


Figure 3.7: Serum creatinine (mg/dl) in preoperative day and 1st and 3rd days postoperative.

Table 3.9: 24 hours urinary albumin (mg/day) in preoperative day and 1st and 3rd days postoperative (data represent means ± SD).

*= Significance at $p < 0.05$

urinary albumin	Pre-operative	First day	Third day
Range	7.0 – 17.50	17.0 – 32.50	24.0 – 41.0
Mean ± SD	12.88 ± 2.88	23.59 ± 4.36	31.16 ± 4.47
F. test	106.836		
p. value	0.001		
Pre-operative & First day	**Pre-operative & Third day**	**First day & Third day**	
0.001*	0.001*	0.001*	

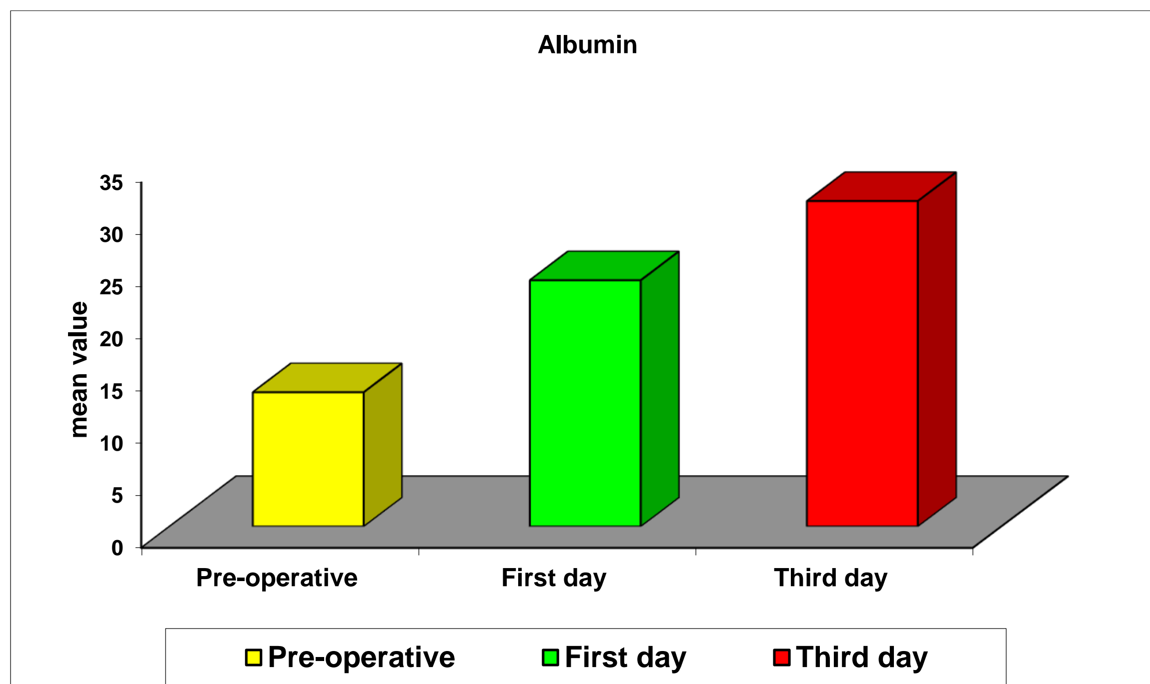


Figure 3.8: 24 hours urinary albumin (mg/day) in preoperative day and 1st and 3rd days postoperative.

Table 3.10: 24 hours urinary glucose (g/day) in preoperative day and 1st and 3rd days postoperative (data represent means ± SD).

*= Significance at $p < 0.05$

urinary glucose	Pre-operative	First day	Third day
Range	0.80 – 0.42	0.35 – 0.85	0.70 – 1.20
Mean ± SD	0.175 ± 0.075	0.565 ± 0.139	0.927± 0.141
F. test	189.407		
p. value	0.001		
Pre-operative & First day	**Pre-operative & Third day**	**First day & Third day**	
0.001*	0.001*	0.001*	

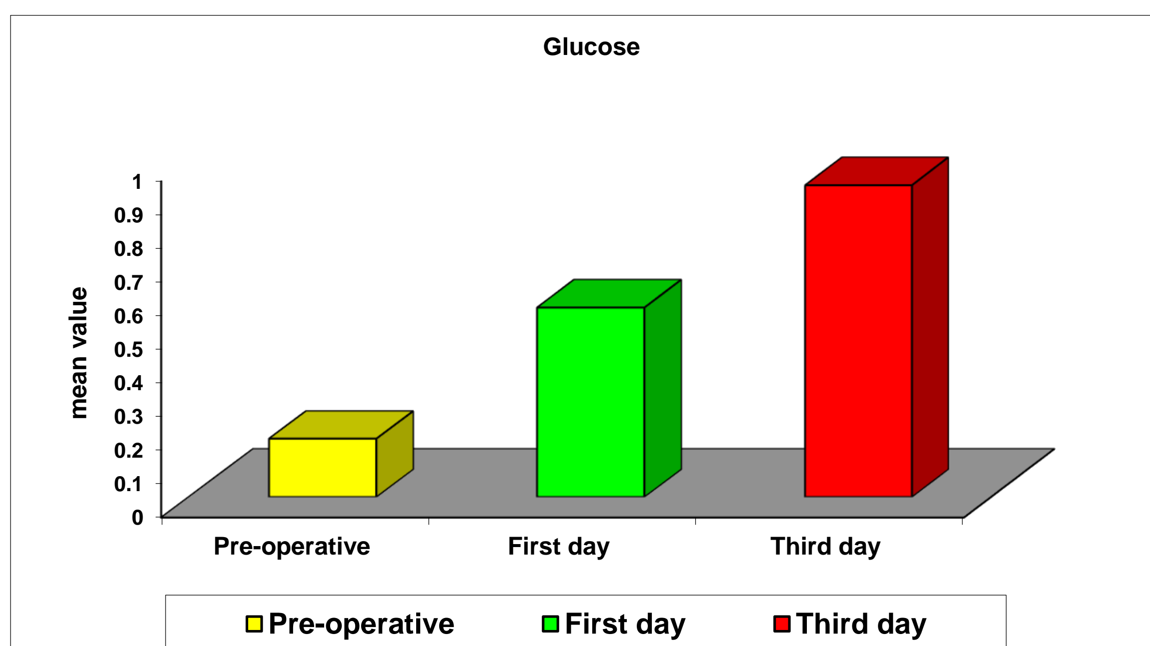


Figure 3.9: 24 hours urinary glucose (g/day) in preoperative day and 1st and 3rd days postoperative.

Table 3.11: 24 hours urinary creatinine (g/day) in preoperative day and 1st and 3rd days postoperative (data represent means ± SD).

*= Significance at $p < 0.05$

Creatinine clearance	Pre-operative		First day	Third day
Range	670 – 1610		660 – 1580	650 – 1560
Mean ± SD	1202.25 ± 208.49		1170.1 ± 204.49	1162.75 ± 203.38
F. test	0.209			
p. value	0.812			
Pre-operative & First day	**Pre-operative & Third day**		**First day & Third day**	
0.623	0.546		0.910	

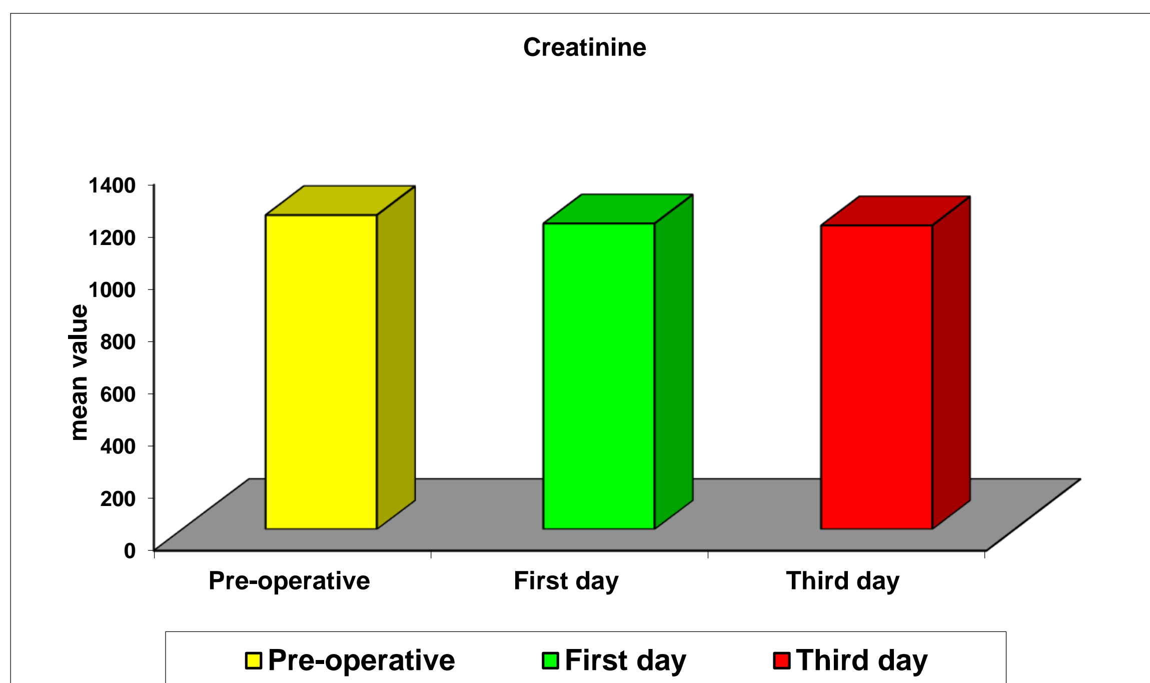


Figure 3.10: 24 hours urinary creatinine (g/day) in preoperative day and 1st and 3rd days postoperative.

Table 3.1: Demographic characteristics of patients, duration of anesthesia and MAC-h exposure to inhalation anesthetic (mean + standard deviation (SD)).

Table 3.2: revealed that the preoperative aspartate aminotransferase (AST) serum level range was (13.50 – 31.0 IU/L) with mean ± SD (19.59± 4.047) ,it was increased significantly on the 1st postoperative day (p. value 0.001) compared to the preoperative value , and also increased significantly on 3rd postoperative day (p. value 0.012) as compared to preoperative value and 1st postoperative day value.

Table 3.3: revealed that the preoperative alanine aminotransferase (ALT) serum level range was (9.30–18.80 IU/L) with mean ± SD (15.045 ± 1.925) ,it was increased significantly on the 1st postoperative day (p. value 0.001) compared to the preoperative value , and also increased significantly on 3rd day postoperative day (p. value 0.003) as compared to preoperative value and 1st postoperative day value.

Table 3.4: revealed that the preoperative alkaline phosphatase (ALP) Serum level range was (78-305 IU/L) with mean ± SD (160.8 ± 48.24) , it was decreased significantly in 1st postoperative day (p.value 0.001) compared to the preoperative value , and also decreased significantly on 3rd postoperative day (p. value 0.309) as compared to the preoperative value (p.value 0.009).

Table 3.5: revealed that the preoperative lactate dehydrogenase (LDH) Serum level range was (197-575 IU/L) with mean $\pm$ SD (362.8 $\pm$ 80.99), it was decreased significantly in 1st postoperative day (p.value0.004) compared to the preoperative value , and also decreased significantly on 3rd postoperative day (p. value 0.017) as compared to 1st postoperative day .

Table 3.6: revealed that the preoperative Serum total bilirubin level range was (0.30-0.70 mg/dl) with mean $\pm$ SD (0.50 $\pm$ 0.103) , it was increased significantly on the 1st postoperative day (p. value 0.001) compared to the preoperative value , and also increased significantly on 3rd postoperative day (p. value 0.028) as compared to preoperative value and 1st postoperative day value.

Table 3.7: revealed that the preoperative blood urea nitrogen (BUN) Serum level range was (9.60-18.0 mg/dl) with mean $\pm$ SD (13.04$\pm$ 1.86) ,it was decreased significantly in 1st postoperative day (p.value 0.001) and non significantly decreased on 3rd day compared to 1st preoperative day (p. value 0.20).

Table 3.8: revealed that the preoperative Serum creatinine level range was (0.40 – 0.80 mg/dl) with mean $\pm$ SD (0.54$\pm$ 0.118), non significantly decreased on 1st and 3rd postoperative day with same value as compared to preoperative value (p.value 0.445).

Table 3.9: revealed that the preoperative urinary albumin level range was (7.0 –17.50 mg/day) with Mean $\pm$ SD (12.88 $\pm$ 2.88), it was increased significantly on the 1st postoperative day (p. value 0.001) compared to the preoperative value , and also increased significantly on 3rd postoperative day (p. value 0.001) as compared to preoperative value and as compared to 1st postoperative day (p.value 0.001).

Table 3.10: revealed that the preoperative urinary glucose level range was (0.80 – 0.42 g/day) with Mean $\pm$ SD (0.175 $\pm$ 0.075) it was increased significantly on the 1st postoperative day (p. value 0.001) compared to the preoperative value and also increased significantly on 3rd postoperative day (p. value 0.001) as compared to preoperative value and as compared to the 1st postoperative day (p.value 0.001).

Table 3.11: revealed that the preoperative urinary creatinine clearance level range was (670 –1610 g/day) with Mean $\pm$ SD (1202.25$\pm$ 208.49) it was non significantly decreased in 1st postoperative day (p.value0.623), and the 3rd postoperative day, as compared to the preoperative value (p.value0.546). and as comparing the 3rd postoperative day with the 1st postoperative day (p.value0.910)

Chapter 4

DISCUSSION

Sevoflurane, fluoromethyl 2,2,2-trifluoro -1- (trifluoromethyl) ethyl ether, is a safe and versatile inhalational anesthetic compared with currently available agents. Of all currently used anesthetics, the physical, pharmacodynamic and pharmacokinetic properties of sevoflurane come closest to that of the ideal anesthetic (61).

Despite mount clinical evidence that supports its safety, the question of the potential adverse effects of sevoflurane on renal function continues to generate some controversy (62).

Sevoflurane undergoes hepatic metabolism with release of inorganic fluoride. Elevated fluoride levels have been associated with renal impairment in patients undergoing methoxyflurane anesthesia raising concerns about the nephrotoxic potential of sevoflurane. This hypothesis was based on the incidence of nephrotoxicity observed at peak plasma fluoride ion levels > 50 µmol/L after methoxyflurane anesthesia (63). However, plasma inorganic fluoride levels > 50 µmol/L were not associated with nephrotoxicity in patients anesthetized with isoflurane or enflurane, which suggest that this toxic threshold can not be applied to other fluorinated anesthetic agents (64).

Although there is no nephrotoxicity after sevoflurane anesthesia in humans with normal kidneys, those with chronically impaired renal function might be at increased risk because of increased fluoride load due to prolonged elimination half-life. Inorganic fluoride concentrations were significantly higher after sevoflurane than after enflurane anesthesia, laboratory measures remained stable throughout the postoperative period.

No patient suffered a permanent deterioration of preexisting renal insufficiency and non required dialysis.

There is no evidence that fluoride released by metabolism of sevoflurane metabolism worsened renal function in these patients with stable, permanent serum creatinine concentrations more than 1.5 mg/dL (65).

Since sevoflurane undergoes hepatic deflurination leading to elevation of plasma fluoride ion, numerous studies have addressed the potential link between elevated plasma fluoride ion levels and nephrotoxicity with the use of sevoflurane. However, fluoride ion nephrotoxicity had not been shown in any of the studies in healthy volunteers (66). Young adults (67), pediatric patients (68), elderly patients (69), pregnant women (70), even after prolonged anesthesia (up to 9 MAC-h) and low flow anesthesia (71) Therefore, the serum fluoride ion concentration after sevoflurane and isoflurane anesthesia was not studied in this work.

Another point to be mentioned is that if one wants to study the effect of defluorination of sevoflurane on renal function. Sevoflurane should be compared with an inhalational anesthetic that undergoes no or very minimal defluorination like desflurane.

Sevoflurane is partly degraded by carbon dioxide absorbents to fluoromethyl-2,2- difluoro-1-(trifluoromethyl) ether (compound A) (72). Compound A is a dose dependent nephrotoxin in rats, with a threshold for microscopic renal injury of 150 to 300 parts per million-hour (ppm- h) (73).

Compound A produces evidence of transient renal injury in rats. The mechanism of compound A renal toxicity is controversial, with the debate focused on the role of the renal cysteine conjugate beta-lyase pathway in the biotransformation of compound A .

The significance of this debate centres on the fact that the beta-lyase pathway is 10- to 30-fold less active in humans than in rats. Therefore, if biotransformation by this pathway is responsible for the production of nephrotoxic metabolites of compound A, humans may be less susceptible to compound A renal toxicity than are rats.

In three studies in human volunteers and one in surgical patients, prolonged (8-hour) sevoflurane exposures and low fresh gas flow rates resulted in significant exposures to compound A. Transient abnormalities were found in biochemical markers of renal injury measured in urine. These studies suggested that sevoflurane can result in renal toxicity mediated by compound A under specific circumstances. However, other studies using prolonged sevoflurane administration at low flow rates did not find evidence of renal injury (74).

The rate at which CO_2 absorbents degrade sevoflurane is dependent on the concentration of the inhalational anesthetic, the fresh gas flow rate (the rate of degradation decreases as the fresh gas flow rate increases), the temperature of the CO_2 absorbent (which in turn is dependent on the quantity of CO_2 passing through) and the water content of the CO_2 absorbents, i.e. it is faster in dry than in wet soda lime or barium hydroxide lime (75,76).

Inflow rate, ventilation, and carbon dioxide production are major determinants of the concentration of Compound A (77).

The concentration of compound A in the anesthesia circuit increases as the fresh gas flow rate decreases (78,79).

Thus, patients who are anesthetized with low flow sevoflurane inhale more compound A. Therefore the use of sevolflurane is safe when it is delivered at high fresh gas flow rates, but the effect of low flow sevoflurane anesthesia on the kidney remains to be clarified in humans.

Low flow anesthesia reduces the costs of anesthesia, decrease atmospheric pollution with inhalation anesthetics and improve the anesthetic gas climate. There are potential risks associated with low flow anesthesia as increased risk of hypoxia and hypercarbia, risk of accumulation of dangerous trace gases, and risk of over or under dosage of inhalational anesthetic.

Modern anesthesia machines meet all technical requirements for safe use of low flow techniques if they are used in conjunction with equipments for monitoring inhaled and exhaled gas concentration.

This study compared the effects of long duration (> 5 hours) low flow (1L/min) sevoflurane anesthesia before and after on human renal and hepatic function.

In the current study (BUN) and serum creatinine were measured to assess global renal function. Twenty four hours urinary albumin, was measured to assess renal glomerular function. While twenty four hours urinary glucose, and 24 hours urinary creatinine were measured to assess renal tubular function.

Assessment of changes in hepatic function was done by measurement of serum (AST), serum (ALT), serum (ALP), serum total bilirubin, and serum (LDH).

This study, was not to measure compound A exposures. This decision was based on the earlier demonstration of a close correlation between sevoflurane MAC-h and inspired compound A levels in surgical patients, thus obviating the need for its measurement (80).

The results of this study demonstrated that BUN and serum creatinine do not increase after low flow sevoflurane anesthesia. This is consistent with previous results from studies done by Obata et al. (81); Eger et al.(82); Ebert et al. (83), Bito et al (84). and Bito and Ikeda (85).

Thus, no abnormality in the standard biomarkers of renal function was seen after long duration, low flow sevoflurane anesthesia.

Regarding the 24-hours urine creatinine there were no significant

differences from baseline values, regarding the 24 hours urine albumin and glucose, there were significant albuminuria, glucosuria with the values in days 1 and 3 postoperatively, significantly different from baseline preanesthetic values.

Kharasch et al (86). Also, found proteinuria and glucosuria after long duration low flow sevoflurane anesthesia. This agrees with results of the present study.

The results of this study regarding urinary albumin and glucose, agrees with the results of Obata et al (81), who demonstrated significant increase in urinary excretion of glucose, albumin and protein, significantly different from baseline values in the 2 postoperative days in patients anesthetized with either low flow sevoflurane or isoflurane for prolonged period.

Ebert et al (87), compared renal responses after anesthesia with desflurane (negligible metabolism), sevoflurane, or intravenous propofol

with low fresh gas flow and anesthesia duration of average 300 min found significant increase in urine glucose, protein, and albumin, occurred similarly in all groups which agrees with the sevoflurane effect in the present study regarding urinary glucose and albumin.

Eger et al (82). Reported that volunteers who were given 3% sevoflurane at a fresh gas flow rate of 2L/min for eight hours showed transient albuminuria, glucosuria and an increase in urinary α -glutathion-S-transferase. In the same setting, Eger et al (88). Found a small amount of albuminuria and increased α-glutathion-S-tranferase after four hours of administration of sevoflurane but no injury after two hours. Based on the findings of these two studies, Eger et al (82,88), concluded that compound A nephrotoxicity is dose dependent in humans as in rats.

In contrast, Ebert et al (89,83), reported that using the same setting neither four nor eight hours sevoflurane anesthesia altered renal function. In the present study albuminuria and glucosuria occurred in the two postoperative days following low flow sevoflurane anesthesia for long duration > 5 hours, but without increase in BUN or serum creatinine.

Kharasch et al (86). Found that proteinuria and glucosuria were extremely common and neither urinary protein nor glucose excretion was different after low flow sevoflurane compared with isoflurane anesthesia, at either 0-24 or 48-72 h after surgery. Kharasch et al (86). Stated that, as proteinuria also occurred with desflurane and even after propofol as mentioned by Ebert et al. (87). Thus, proteinuria after anesthesia and surgery is a common finding and does not per se indicate renal toxicity.

In the present study, regarding the liver function tests (as indicated by serum AST, serum ALT, serum total bilirubin, serum ALP, and serum LDH in the two postoperative days in patients anesthetized with long

duration low flow sevoflurane compared with preanesthetic liver function both serum AST and ALT were increased significantly but within the normal range, and regarding serum total bilirubin, it increased significantly but within the normal range.

Regarding serum alkaline phosphatase ALP and serum lactate dehydrogenase LDH both are decreased progressively significantly from preanesthesia till the third postoperative day.

Kharasch et al (86). Found no difference between anesthetic groups and within same group in long duration low flow sevoflurane and isoflurane anesthesia regarding serum AST and ALT in 24 or 72 hours postoperatively which agrees with the present study.

Obata et al (81). Demonstrated that hepatic function values increased on day 5 (not included in the present study) after low flow sevoflurane anesthesia but these increases were not significantly different as compared with low flow isoflurane anesthesia. Therefore, prolonged low flow sevoflurane anesthesia is not likely to cause hepatotoxicity as mentioned by Obata et al (81). And this agrees with the results of the present study.

Bito and Ikeda (90), showed that total bilirubin, AST and ALT increased after sevoflurane anesthesia, this agrees with the results of present study.

Al-Sayed and Soliman (91), Compared between long duration sevoflurane and isoflurane anesthesia on hepatic function and found no hepatic injury as defined by normal ALT and AST levels postoperatively.

Chapter 5

CONCLUSION AND RECOMMENDATIONS

6.1. CONCLUSION:

The current study showed no significant differences, between the renal effects of sevoflurane in surgical patients undergoing long duration low flow anesthesia. Renal effects were evaluated by measuring serum creatinine, BUN and urinary creatinine, albumin, and glucose excretion. albuminuria and glucosuria were common and non specific postoperative findings.

Also, there were no significant differences in liver function before and after surgery with low flow sevoflurane.

Liver function was assessed by using serum AST, ALT, ALP, LDH and total bilirubin.

From this work it is concluded that long duration low flow sevoflurane anesthesia seems to be safe regarding hepatic and renal functions in humans.

6.2. RECOMMENDATIONS:

Long durationlow flow sevoflurane anesthesia appears to be safe as long duration low flow anesthesia regarding hepatic and renal functions in humans. However, concerns regarding the degradation of inhalational anesthetics in general by CO_2 absorbents to toxic compounds may still be a point of debate. The widespread application of absorbents that minimally degrade sevoflurane to compound A or desflurane to corbon monoxide would eliminate any potential hazard from these toxic compounds (92,93). Such absorbents do not contain either sodium hydroxide or potassium hydroxide,both of which appear to enhance the production of compound A and carbon monoxide.

Also, the generation of breakdown products during sevoflurane anesthesia can be circumvented by the use of molecular sieves as an alternative to soda lime(94). When used in a simulated low-flow closed-circuit anesthetic system, molecular sieves were as efficient as soda lime in the removal of CO_2.

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الـملخص العربي

يعـــد الســـيفوفلورين (فلورميثيـــل بـــولى فلوروأيزوبروبايـــل إيثـــر), واحـــداً مـــن جيـــل جديـــد مـــن أدويـــة التخـــدير الكلـــى المستنشـــقة, وهـــو يتميـــز بقابليـــة أقـــل للـــذوبان فـــى الـــدم عـــن أدويـــة أخـــري مثـــل ايزوفلـــورين, إنفلـــورين أو هـــالوثين , ويتحلـــل الســـيفوفلورين عـــن طريـــق جيـــر الصـــودا وجيـــر هيدروكســـيد البـــاريوم وينـــتج عـــن تحللـــه مـــواد منهـــا مركـــب أ و يعتمـــد معـــدل تحلـــل الســـيفوفلورين عـــن طريـــق ماصـــات ثـــاني أكســـيد الكربـــون علـــى تركيـــز المخـــدر , معـــدل تـــدفق الغـــاز النقـــي , حـــرارة ممـــتص ثـــاني أكســـيد الكربـــون وكميـــة المـــاء بـــه و نوعيتـــه, فيـــزداد معدل تحلل السيفوفلوين باستخدام تدفق منخفض من الغاز النقي.

عقـــارى الســـيفوفلورين يثـــبط انقباضـــية عضـــلة القلـــب ويثـــبط التـــنفس و يعكـــس انقبـــاض الشـــعب الهوائيـــة ,الســـيفوفلورين لا يهـــيج الممـــرات الهوائيـــة بالمقارنة ببعض أدوية المستنشقة كعقار الأيزوفلورين .

الســـيفوفلورين يـــؤدى إلـــى زيـــادة بســـيطة فـــى تـــدفق الـــدم إلـــى المـــخ ممـــا يـــؤدى إلـــى زيـــادة الضـــغط داخـــل الجمجمـــة ولكنـــه يحـــافظ علـــى التنظـــيم الـــذاتي لتـــدفق الـــدم المخي .

التخـــدير باســـتخدام غـــاز نقـــي مـــنخفض التـــدفق يقلـــل مـــن نفقـــات التخـــدير ومـــن التلـــوث البيئـــي ويحســـن مـــن منـــاخ الغـــاز التخـــديري المستنشـــق, ولكنـــه يزيـــد مـــن تحلـــل الســـيفوفلورين إلـــى مركـــب أ ومـــن هـــذا المنطلـــق فـــإن غـــرض هـــذا البحـــث هـــو تقيـــيم تـــأثير عقـــاري الســـيفوفلورين باســـتخدام التـــدفق المـــنخفض بعـــد عمليـــات جراحية طويلة المدة, على وظائف الكلى و الكبد فى الإنسان.

وقـــد أجريـــت هـــذه الدراســـة علـــى عشـــرين مـــريض بـــالغ مـــن الجنســـين وقـــد استخدم السيفوفلورين كغاز تخديري مستنشق

وقد تم دراسة تأثير عقاري السيفوفلورين على وظائف الكلى والكبد باستخدام التحاليل المعملية وتبين عدم وجود تأثير واضح على وظائف الكلى والكبد ومن هذا نستنتج أن التخدير باستخدام عقار السيفوفلورين والتدفق المنخفض طويل المدة ليس له أي تأثير سام على الكلى أو الكبد في المرضى الجراحيين ناتج عن استخدامه.