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EFFECT OF LONG DURATION SEVOFLURANE ANESTHESIA ON LIVER FUNCTION

Abdalla M. Jarari[1], Awad M. Abdelstar Alhasnony[2], Nouh M.H. Aljarari[3], Ayman S. Abdelsalam[2], Mustafa Younis[1], Osama Hussein Al Deeb[4] Shakila Srikumar[5] F.G. Dawoodi[5] Yupa Min[5] Abdul Rehaman Said[5], Sathish Kumar Thammiraju[6] Avinash K Rawal[7] and Peela Jagannadha Rao[7*]

[1]Dept. of Biochemistry, Faculty of Medicine, University of Benghazi.Libya (First author).
[2]Department of Anesthesia and Surgery, Faculty of Medicine, Tobruk Medical Center.
[3]Department of Pharmacology, Faculty of Medicine, Benghazi University.
[4]Department of Biochemistry, Faculty of Medicine, Omar Almokhtar University, AL Beida, Libya.
[5]Faculty of Medicine, Quest International University Perak, Ipoh, Malaysia.
[6]Department of Critical Care, Apollo Hospitals, Secunderabad, Telangana, India.
[7]Department of Biochemistry and Medical Genetics. School of Medicine, St Matthews University, Grand Cayman, Cayman Islands.

***Corresponding Author: Dr. Peela Jagannadha Rao**
Department of Biochemistry and Medical Genetics, School of Medicine, St Matthews University, Regatta Office Park, Leeward 3, Grand Cayman, KY1-1204, Cayman Islands.

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ABSTRACT

Background: Sevoflurane is an inhalational anesthetic 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%. Sevoflurane can be administered to patients with normal or mild-to-moderately impaired hepatic functions. However, patients with severe hepatic dysfunction were not investigated. **Objective:** The present study was conducted to evaluate liver function of the patients who underwent sevoflurane anesthesia for long durations. **Material and methods**: In this prospective study, 20 patients undergoing surgery with sevoflurane as anesthetic were selected. Serum aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and total bilirubin was measured by authenticated methods by using automated system (VITROS 2005, USA) preoperatively and 1st and 3rd day postoperatively. **Results:** Aspartate aminotransferase level significantly elevated on 1st postoperative day ($p<0.001$) and on 3rd postoperative day ($p=0.012$) as compared to preoperative value.Alanine aminotransferase level increased significantly on the1stpostoperative day ($p<0.001$) and on 3rd day postoperative day ($p=0.003$). Alkaline phosphatase decreased significantly in 1st postoperative day ($p<0.001$) and on 3rd postoperative day ($p=0.309$). Lactate dehydrogenase was decreased significantly in 1st postoperative day ($p=0.004$) and on 3rd postoperative day ($p=0.017$). Serum total bilirubin level was increased significantly on the 1st postoperative day ($p<0.001$) and on 3rd postoperative day ($p=0.028$). **Conclusion:** According to this study the liver enzymes and bilirubin were raised but not above reference range. Aspartate and Alanine amino transferase shown decline on 3rd day when compared to 1st postoperative day. Hence long duration anesthesia by sevoflurane is relatively safe and not hepatotoxic.

INTRODUCTION

Since the clinical introduction of halothane (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 been centered upon the development of compounds with the following main properties.[3,4] (i) rapid and tolerable induction of, and recovery from, anesthesia, (ii) rapid adjustment of the depth of anesthesia. (iii) adequate skeletal muscle relaxation, (iv) wide margin between concentrations producing the required pharmacological effect and those producing toxicity and (v) absence of toxic effects or other adverse events at normal doses.

Sevoflurane is a newer halogenated anesthetic, introduced in the year, 1995. The low solubility of sevoflurane in the blood would have suggest that alveolar concentrations must rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent.[5]

The rapid pulmonary clearance of sevoflurane minimizes the amount of anesthetic available for metabolism. In humans, approximately five percent of sevoflurane is metabolized by cytochrome P450 2E1 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. None other metabolic pathways for sevoflurane have been identified. It is the only fluorinated volatile anesthetic that will not be metabolized to trifluoracetic acid.[6]

MATERIALS AND METHODS

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).

The patients who were scheduled for surgery of suspected duration >4 hours at Tobruk Medical center were included in the study. **Inclusion Criteria**

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

Exclusion Criteria

Any of the following was 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.

Anesthetic management

A standard technique of anesthesia was used for all patients.

A) Preoperative preparation

- Full 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.
- A10 ml blood sample was collected from each patient preoperatively for base line laboratory evaluation, the following parameters were measured.

(b) Blood investigations

- Aspartate aminotransferase (AST).
- Alanine aminotransferase (ALT).
- Alkaline phosphatase (ALP).
- Lactate dehydrogenase (LDH).
- Total bilirubin.

Preanesthetic medication

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

(C) Preinduction

- Prior to induction, an intravenous infusion started and the patient received at least 0.5 ml/kg Ringer lactate for each hour 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 every patient.
- Pre-oxygenation of at least 3 minutes was allowed via face mask with 100% Complete medical history was taken from each patient. 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 orotracheal 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 introduction of anesthesia, both lungs were mechanically ventilated initially with a tidal volume of 7 to 10 ml/kg, with a ventilatory rate of 12 breaths/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 pancuronium top up doses. Proper analgesia was maintained throughout the operation with fentanyl 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, after which 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 O_2 concentration in the inspiratory limb at more than 30%. The inhalational anesthetic concentrations were adjusted to maintain systolic blood pressure with in 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.
Two samples of venous blood (10ml each) were taken at 1st and 3rd day after anesthesia for measurement of serum AST, ALT, LDH, ALP, and total bilirubin.

The measurements of AST, ALT, ALP, LDH and total bilirubin were done using fully automated system (VITROS 2005, USA)

(H) Monitoring of inhalation anesthetic concentration using a pre-calibrated multi gas analyzer (built in the anesthesia machine). The alveolar concentrations (F_A) of volatile anesthetics were recorded at 10 min. 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 dividing the mean of all readings of (F_A) by the (MAC) value of the inhalational anesthetic used and multiplying the result by the duration of anesthesia in hours.

STATISTICAL ANALYSIS

Data were statistically described in terms of range, mean, standard deviation (SD), median and other parameters by using SPSS software.

RESULTS

Demographic characteristics of patients, duration of anesthesia and MAC-h exposure to inhalation anesthetic (mean±SD) are shown in table 1.

The results are summarized in table 2. The preoperative serum AST 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<0.001) compared to the preoperative value, and also increased significantly on 3rd postoperative day (p=0.012) as compared to preoperative value and 1st postoperative day value.

The preoperative serum ALT level range was (9.30–18.80 IU/L) with mean±SD (15.045±1.925). It was increased significantly on the1stpostoperative day (p. value 0.001) compared to the preoperative value, and also increased significantly on 3rd day postoperative day (p=0.003) compared to preoperative value and 1st postoperative day value.

The preoperative serum ALP level range was (78-305 IU/L) with mean±SD (160.8±48.24). It was decreased significantly on the 1st postoperative day (p<0.001) compared to the preoperative value, and also decreased significantly on the 3rd postoperative day (p<0.309) compared to the preoperative value (p<0.009).

The preoperative serum LDH level range was (197-575 IU/L) with mean±SD (362.8±80.99). It was decreased significantly in 1st postoperative day (p=0.004) compared to the pre operative value, and also decreased significantly on 3rd postoperative day (p=0.017) compared to 1st postoperative day.

The preoperative serum total bilirubin level range was (0.30-0.70 mg/dl) with mean±SD (0.50±0.103). It was increased significantly on the 1st postoperative day (p<0.001) compared to the preoperative value, and also increased significantly on 3rd postoperative day (p=0.028) compared to preoperative value and 1st postoperative day value.

Table 1: Demographic characteristics of patients, duration of anesthesia and MAC-h exposure to inhalation anesthetic (mean ± standard deviation (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 2: The values of LFT before and after administration of sevoflurane and their significance. (AST:Aspartate amino transferase, ALT: Alanine amino transferase, ALP: Alkalline Phosphatase and LDH: Lactate dehydrogenase.)

	Pre operative	Post operative Day 1	Post operative Day 3
AST	19.59±4.01	32.20±4.29	28.94± 3.50
p-Value		0.001	0.012
ALT	15.04± 1.95	29.01± 4.47	25.32± 4.41
p-Value		0.001	0.003
ALP	160.80±48.24	109.33±4.24	123.47±39.51

p-Value		0.009	0.309
LDH	362.8± 80.99	294.30±75.69	238.00±59.65
p-Value		0.001	0.017
BILIRUBIN	0.50±0.10	0.80±0.15	0.71±0.13
p-Value		0.001	0.028

DISCUSSION

Sevoflurane, the most recent halogenated anesthetic is available since 1995. It has many desirable clinical properties, including a non pungent odor and low solubility in blood, which aide in rapid induction and recovery.

It has been observed before the administration of sevolflurane is not associated with elevated ALT and AST levels.[7] Unlike the older halogenated anaesthetic agents, sevoflurane metabolism does not result in the formation of trifluoroacetic acid (TFA), because of which it is considered to be less hepatotoxic.[8,9] Instead, sevoflurane metabolism results in the formation of hexafluoroisopropanol (HFIP), which has significantly less protein binding capability than TFA. Further, HFIP does not accumulate and rapidly undergoes glucuronidation, forming HFIP-glucuronide, which is water soluble, and is predominantly excreted in the urine within 12 hours of anesthesia and cannot be detected beyond 2 days.[10-12] However, TFA can be detected in urine for up to 12 days after 75 minutes of anesthesia.[13-15]

This study was conducted to compare the effects of long duration (>5 hours) low flow (1L/min) sevoflurane anesthesia on human renal and hepatic 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.[16]

Studies have shown that sevoflurane has a low hepatotoxic potential.[17-19] However, there were other case studies reported severe liver toxocity with sevoflurane.[20-22]

Obata et al. demonstrated that hepatic function values increased on day 5 (not included in the present study) after low flow sevoflurane anesthesia compared with low flow isoflurane anesthesia. Similar to our study but these increments were not significantly different as findings, prolonged low flow sevoflurane anesthesia was not likely to cause hepatotoxicity in the study by Obata et al.[23] Further, Bito and Ikeda[24] demonstrated that total bilirubin, AST and ALT increased after sevoflurane anesthesia. Al-Sayed and Soliman[25] 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.

Further, sevoflurane seems to be a suitable anaesthetic for patients with previous exposure to other halogenated anaesthetics or hepatic disease.[26-28] Studies have also demonstrated that sevoflurane may be a viable option for anaesthesia in large size surgeries and liver transplants, where postoperative liver dysfunction could be detrimental to patients. It is further reassuring that sevoflurane may even exert a protective effect on hepatic ischemia/reperfusion injury, which is a frequently encountered problem in hepatic surgery,[27,29,30] although these findings have to be confirmed in larger and varied patient populations.

CONCLUSION

According to this study the liver enzymes and bilirubin were raised but not above reference range. Aspartate and Alanine amino transferase shown decline on 3rd day when compared to 1st postoperative day. Hence long duration anesthesia by sevoflurane is relatively safe and not hepatotoxic. Therefore, we conclude that sevoflurane may be the anesthetic of choice in prolonged surgeries. However, the sample size in our study was small, and therefore larger, randomized controlled studies are required to confirm these observations.

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