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COMPARATIVE HISTOLOGICAL AND CLINCAL STUDY OF TWO INHALAR ANAESTHETICS

*Mahmoud A.A.Masoud * Nasr El-Din M. Siam**;*
*Karam M. El-Rouby**; Emad M.A.Emam***

Histology* and Anaesthesia & Intensive care Departments Faculty of Medicine Al-Azhar University**

ABSTRACT

Sevoflurane (Fluromethyl 1,1,1,3,3,3, Hexafluoro isopropyl ether) is one of the newly introduced inhalational Anaesthesia. It is considered as a rapid acting and potent inhalation anaesthetic agent. It is metabolized in the body into non-toxic substances. It also has a rapid uptake and elimination rate due to its low blood gas partition coefficient, which approaches that of nitrous oxide. Interest in sevoflurane has increased with the recent emphasis for out patient surgery because it has a mild ethereal odor and low solubility in blood; lipid; and tissues. So, it is suggested as being anaesthetic of the future. This study is designed to illustrate the histological and the clinical effects of sevoflurane in comparison with isoflurane as a common inhalational anaesthetic agent, regarding the haemodynamic, hepatic and renal effects. The clinical study included 80 adult persons of both sexes, during surgical operations. The patients were divided into 2 groups, 40 persons each. Group I: received sevoflurane and group II: received isoflurane. Routine examinations; investigations; Liver and renal function tests were done just before induction and after 2 hours; 4 hours; 24 hours and 7 days of recovery. The experimental study was done on 90 rats of both sexes. They were divided into 3 groups: 30 rats each. Group (A): control group, group (B): Anaesthetized with sevoflurane and group (C): Anaesthetized with isoflurane. Each group was subdivided into 2 subgroups, 15 rats. The 1st subgroup was sacrificed after 24 hours of exposure. The 2nd subgroup was sacrificed after 7 days from the start of exposure. The rats were sacrificed and their blood was investigated. Liver and kidney structure were evaluated histologically and histochemically. Our results revealed that, sevoflurane and isoflurane had non-significant post-operative clinical manifestations and non-significant changes on the liver or kidney function tests. Histological examination of liver revealed normal hepatocytes and mild congestion in blood sinusoids and central veins in sevoflurane group. While, liver sections in isoflurane group showed more congestion, dilatation and cellular infiltration. . Histological examination of the kidney revealed no changes in the sevoflurane group. In contrast, isoflurane group had congestion and cellular infiltration of renal parenchyma. All changes almost completely disappeared after seven days of recovery. Histochemical results revealed significant decrease in PAS positive material and succinic dehydrogenase enzyme activity in hepatocytes and renal tubules, mainly in isoflurane than sevoflurane groups. While, acid and alkaline phosphatase enzymes activity showed non-significant decrease in both drugs. All changes were non-significant after seven days of recovery. This study proved that the sevoflurane had no harmful effect and can be considered as a safe inhalational drug.

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Introduction

There is an intense need for incr -easing safety for almost all body organs after Anaesthesia. So, the search for improved inhalational agents had to be continued.

Sevoflurane (Fluromethyl 1,1,1, 3,3,3, Hexafluoro isopropyl ether) is the most recent rapid acting and potent inhalation anaesthetic agent. It is metab -olized in the body into hexafluro-isopr -opyl alcohol, carbon dioxide and fluo -ride ion, and has rapid uptake and elimination due to its low blood gas partition coefficient, (Wong and Lerm -an, 1992). Interest in sevoflurane has increased with the recent emphasis on outpatient surgery because it has mild ethereal odour and low solubility in blood; lipid; and tissues. Also, it has no effect on myocardial blood flow or arrhythmogenicity of heart, and recov -ery from this anaesthetic agent is rapid, (Malviya and Lerman, 1990 and Takahata et al, 1995). Isoflurane (1-Chloro-2, 2,2-Trifluoro-ethyl Difluorom -ethyl ether) was approved for clinical use in 1980 and it is considered as the most widely used potent inhaled anaesthetic agent in North America, (Forrest, 1983). It is metabolized into difluro-methanol and trifluro-acetic acid, which break down to formic acid and fluoride. It has minimal hepatot -oxicity, arrhythmogenicity and is less depressant to circulation. It has pungent odour and respiratory depressant effect that resembles some volatile anaesthe -tics, which limit its use as induction agents. It rarely causes convulsions or cerebral effect, (Eger, 1984).

To be useful clinically an anaesthetic must be devoid of toxic effects, (Kenna and Jones 1995). So, this study is designed to illustrate the histological and clinical effect of sevoflurane in comparison with isoflurane as a common inhalational anaesthetic agent. Haemodynamic, hepatic and renal affects were evaluated on human and albino rats.

Material and Methods

A- Patients:

This study was conducted on 80 adult patients of both sexes. Their age ranged from 18-48 years old and their body weight ranged from 60-90 Kg. Pre-operative history, routine examin -ation, hemoglobin concentration, blood gases (O2 saturation & End-tidal CO2); kidney and liver function tests, Electro-cardiogram (ECG), heart rate (HR) and mean blood pressure (MBP) were recorded for each patient. All patients had no previous operations and they were free from liver, kidney, chest, heart or endocrine diseases and were not suffering from hematological or hemorrhagic disorders. All of them gave formal consents. They were subjected to routine pre-operative preparation and examination for elective surgery.

The patients were divided into two groups, 40 patients for each group.

Group I: received **1** MAC (Minimum Alveolar Concentration) of 2% sevofl -urane for 2 hours.

Group II: received **1** MAC of 1.15% isoflurane for 2 hours.

Routine induction; maintenance; intravenous lactated ringer solution; blood pressure and ECG were performed during the operations. Also, routine post-operative recovery was done.

Post-operative examination and investigations were done after 2; 4; 24 hours and 7 days of operations for:

1-Hemodynamic study: ECG; HR and MBP.

2-Liver function tests: Serum glutamic oxalo acetic transaminase (SGOT) and Serum glutamic pyruvic transaminase (SGPT).

3-Kidney function tests: blood urea (U) and Serum creatinine (C).
4-Arterial blood sampling: O2 saturation and End-tidal- CO2.

B-Experimental animals:

Ninety adult albino rats of both sexes an average weight 180-200 gm. were included in this study and they were classified into 3 groups, 30 rats for each group.

Group (A): Control group, the rats of this group were exposed to 40% oxygen (4L/ min.), and they were subdivided into two subgroups.

Subgroup (A1): 15 rats exposed to oxygen for two hours, and were sacrificed after 24 hours.

Subgroup (A2): 15 rats exposed to oxygen for 2 hours, and sacrificed after 7 days of last exposure (recovery group).

Group (B): Anaesthetized with **1** MAC of sevoflurane 2% with gas flow of 4L/ min. in 40% oxygen, and they were subdivided into two subgroups.

Subgroup (B1): 15 rats exposed to sevoflurane for two hours, and sacrificed after 24 hours.

Subgroup (B2): 15 rats exposed to sevoflurane for two hours, and sacrificed after 7 days of last exposure (recovery group).

Group (C): Anaesthetized with 1 MAC of isoflurane 1.15% with gas flow of 4L/min. in 40% oxygen, and they were subdivided into two subgroups.

Subgroup (C1): 15 rats exposed to isoflurane for two hours, and sacrificed after 24 hours.

Subgroup (C2): 15 rats exposed to isoflurane for two hours, and sacrificed after 7 days of last exposure (recovery group).

Anaesthesia was administrated from temperature compensated vapori - zers and maintained through the experiment for two hours at stage 3 of anaesthesia as assessed by pupil size, position response to light, and tone of the jaw muscles (Egar and Johnson, 1987). At the end of this period the anaesthesia was discontinued and the rats were given air to breath, and returned to their cages. Blood samples were collected before, after two hours and after 7 days of anaesthesia. The rats were sacrificed, liver and kidney specimens were taken and routinely prepared for paraffin and frozen sectioning, and stained with Hemat - oxylin & Eosin for histological study and PAS stain, acid phosphates, alkaline phosphates and Nitro-blue tetrazolium for histochemical study (Drury and Walington, 1980 and Seligman and Rutenburg, 1951).

Quantitative analysis was done by computerized image analysis, and the statistical evaluation was performed using the student's t-test.

Results

Clinical results:

A. Hemodynamic data: (table, 1): There was no significant difference in pre- and post-operative heart rate and blood pressure between group I & II. While, there was significant difference in Heart rate during the operations and at the first 30 minuets of Intra-oprative blood pressure. Also, there was no significant difference in pre-, intra- and post-operative Electro-cardiogram of either group.

B. Arterial blood gases: There were no changes in O2 blood saturation and End-tidal-CO2 in pre-, intra- and post-operative blood samples of both groups.

C. Liver function tests: There was no significant difference in pre and post-operative serum SGOT and SGPT of the two groups, (table 2&3).

D. Kidney function tests: As shown in (table, 4 & 5), there was no significant difference in pre- and post-operative blood urea and serum creatinine levels between the two groups.

E. Urine analysis: Albumin was detected in the urine of isoflurane group (30 mg/dl) after 24 hours of operation and disappeared after 7 days. While, there was no albumin in the urine of sevoflurane group. Glucose was not detected in the urine of both groups.

Experimental results:

Liver function tests of experim - ental rats showed no significant differe - nce in serum SGOT and SGPT levels between control and treated groups, after 24 hours and 7 days of operation , (table 6&7).

Kidney function testes showed no significant difference in blood urea and serum creatinine levels between control and treated groups, after 24 hours and 7 days of operation, (table 8&9).

Histological examination of liver sections in sevoflurane treated group after 24 hours of anaesthesia showed normal hepatocytes and mild congestion in blood sinusoids and central veins. After 7 days of recovery , no histolo - gical change could be detected in liver sections. Liver sections of isoflurane treated group after 24 hours of anaest - hesia, showed hypochromic stained hepatocytes, cellular infiltration and congestion in blood sinusoids and around central veins. After 7 days of recovery, mild cellular infiltration and congested blood vessels were still present (Fig.1).

Histological examination of kidney sections in sevoflurane treated group, after 24 hours and 7 days of recovery showed normal renal corpuscles and tubules. Kidney sections of isoflurane treated group after 24 hours of anaesthesia, showed congestion and cellular infiltration between the renal tubules. These changes were not noticed in the sections after 7 days of recovery (Fig.2).

Histochemical results:

The optical density value repres - enting the mucopolysaccharide content in liver sections of sevoflurane group after 24 hours of anaethesia was significantly less than control group. While, the optical density of isoflurane group was significantly less than control and sevoflurane groups (Fig.3 and table 10). After 7 days of recovery, the difference between the mean of three groups was not statistically significant.

The optical density value obtained from PAS-stained kidney sections of sevoflurane group after 24 hours of anaesthesia was significantly less than those of the control group. While, the optical density of isoflurane group was significantly less than control and sevoflurane groups (Fig.4 and table 11). After 7 days of recovery, there was no significant change between the means of the three groups.

There was no change in the optical density value of acid and alkaline phosp -hates enzymes activity in liver and kidney sections of sevoflurane and isofl -urane groups after 24 hours and 7 days of recovery in comparison to control group (Fig. 5,6,7,8 and table 10&11).

The optical density value indicating the succinic dehydrogenase enzyme activity in liver and kidney sections of sevoflurane group after 24 hours of anaethesia was significantly less than control group. While, the optical density value of isoflurane group was significantly less than control and sevoflurane groups (Fig.9&10 and table10&11). After 7 days of recovery there was no statistically significant difference between the means of the three groups.

Table (1): Heart rate (HR) and blood pressure (BP), after sevoflurane and isoflurane anaesthesia.

Timing	Group I Sevoflurane		Group II Isoflurane		t-test	Group I Sevoflurane		Group II Isoflurane		t-test
	Mean HR	S.D	Mean HR	S.D		Mean BP	S.D	Mean BP	S.D	
Pre-operative	75.45	4.14	75.73	4.24	0.8353 $	88.89	7.22	90.33	7.51	0.4156 $
Intra-opertive										
10 min	71.85	3.89	85.45	5.87	0.0002 *	81.85	6.58	93.73	6.79	0.0001 *
20 min	71.35	3.51	81.35	6.28	0.0002 *	81.7	6.87	88.13	7.29	0.0003 *
30 min	70.8	3.32	80.48	6.2	0.0003 *	80.63	6.33	86.13	7.45	0.0017 *
40 min	71.38	4.09	81.3	6.06	0.0001 *	81.95	6.15	84.9	6.69	0.0546 $
50 min	71.1	3.03	80.95	6.28	0.0001 *	81.1	5.87	83.28	6.14	0.1091 $
60 min	71.43	3.23	80.1	6.48	0.0002 *	80.85	6.09	82.85	6.32	0.1545 $
70 min	71.15	2.91	80.28	6.40	0.0001 *	79.93	6.66	82.23	5.57	0.1029 $
80 min	70.4	3.26	80.38	6.48	0.0001 *	80.13	6.69	81.48	5.56	0.3338 $
90 min	70.7	3.16	79.87	6.37	0.0002 *	80	6.52	80.8	5.78	0.5634 $
100 min	70.88	3.25	79.58	6.12	0.0001 *	80.15	6.81	80.65	6.38	0.7556 $
110 min	71.9	2.85	79.83	5.95	0.0001 *	81.15	6.67	80.08	5.26	0.4672 $
120 min	73.19	3.32	79	6.41	0.0002 *	81.76	6.56	80.62	6.18	0.4373 $
Post-operative										
2 hours	78.1	3.48	79.6	5.22	0.135 $	87.18	6.25	86.15	6.32	0.468 $
4 hours	75.03	3.98	76.8	5.42	0.99 $	89.38	6.92	88.83	7	0.725 $
24 hours	75.4	3.98	75.68	4.12	0.8521 $	88.85	7.21	90.13	7.42	0.3981 $

(P-Value is significant at <0.05 level and non-significant at >0.05)
* HR and BP are significant less in sevoflurane than isoflurane.
$ No significant change between sevoflurane and isoflurane group.

Table (2): Comparison between sevoflurane and isoflurane as regards serum SGOT level (U/L).

	Group I Sevoflurane		Group II Isoflurane		t-test
	Mean	S. D	Mean	S. D	
Pre-operative	16.60	4.47	16.05	4.72	0.594
2 hr. post-operative	16.53	4.27	15.63	4.72	0.374
4 hr. post-operative	16.55	4.45	16.23	5.09	0.765
24 hr. post-operative	20.43	6.42	16.23	5.09	0.058
7 days post-operative	18.71	5.37	15.97	4.92	0.089

There was no significant difference between the two groups.
(P- Value is >0.05)

Table (3): Comparison between sevoflurane and isoflurane as regards serum SGPT level (U/L).

	Group I Sevoflurane		Group II Isoflurane		t-test
	Mean	S. D	Mean	S. D	
Pre-operative	19.40	4.56	18.9	4.92	0.639
2 hr. post-operative	19.18	4.29	18.65	4.82	0.608
4 hr. post-operative	19.43	4.67	18.7	5.08	0.508
24 hr. post-operative	20.98	4.93	19.53	5.42	0.038
7 days post-operative	20.49	4.84	18.96	5.25	0.074

There was no significant difference between the two groups.
(P- Value is >0.05)

Table (4): Comparison between sevoflurane and isoflurane as regards blood urea (mg/dl).

	Group I Sevoflurane		Group II Isoflurane		t-test
	Mean	S. D	Mean	S. D	
Pre-operative	24.6	3.83	23.23	4.63	0.152
2 hr. post-operative	24.83	4.31	23.45	3.21	0.110
4 hr. post-operative	24.75	3.84	22.95	4.69	0.064
24 hr. post-operative	25.58	4.23	23.7	5.49	0.091
7 days post-operative	24.74	4.71	24.37	4.98	0.162

There was no significant difference between the two groups.
(P- Value is >0.05)

Table (5): Comparison between sevoflurane and isoflurane as regards serum creatinine level (mg/dl).

	Group I Sevoflurane		Group II Isoflurane		t-test
	Mean	S. D	Mean	S. D	
Pre-operative	0.7970.810	0.126	0.79	0.101	0.793
2 hr. post-operative	0.819	0.098	0.773	0.091	0.083
4 hr. post-operative	0.835	0.096	0.789	1.40	0.167
24 hr. post-operative	0.815	0.105	0.116	1.72	0.090
7 days post-operative		0.110	0.089	1.74	0.085

There was no significant difference between the two groups.
(P- Value is >0.05)

Table (6): Comparison between the experimental groups as regards SGOT level (U/L).

	24 hr. after exposure			7 days after exposure		
	Control	Sevo.	Iso.	Control	Sevo.	Iso.
Number	15	15	15	15	15	15
Range	13-30			13-30		
Mean	21.11	20.93	23.02	20.59	16.12	18.58
S. D	3.95	3.15	3.39	4.1	3.1	4.37
t-test	0.2089			0.0728		

P-Value is non significant (P>0.05)

Table (7): Comparison between the experimental groups as regards SGPT level (U/L).

	24 hr. after exposure			7 days after exposure		
	Control	Sevo.	Iso.	Control	Sevo.	Iso.
Number	15	15	15	15	15	15
Range	7.9-18.4			7.9-18.4		
Mean	14.15	16.27	16.6	12.69	12.44	13.05
S. D	3.22	3.88	2.87	1.92	1.76	1.25
t-test	0.6029			0.1065		

P-Value is non significant (P>0.05)

Table (8): Comparison between the experimental groups as regards blood urea level (mg/dl).

	24 hr. after exposure			7 days after exposure		
	Control	Sevo.	Iso.	Control	Sevo.	Iso.
Number	15	15	15	15	15	15
Range	18.7-40			18.7-40		
Mean	27.51	25.07	28.53	27.64	27.99	30.53
S. D	5.87	4.1	4.36	4.79	5.53	4.56
t-test	0.1442			0.2340		

P-Value is non significant (P>0.05)

Table (9): Comparison between the experimental groups as regards serum creatinine level (mg/dl).

	24 hr. after exposure			7 days after exposure		
	Control	Sevo.	Iso.	Control	Sevo.	Iso.
Number Range Mean S. D	15 0.8-1.2 0.9 0.1	15 0.92 0.10	15 0.94 0.14	15 0.8-1.2 0.90 0.1	15 0.84 0.05	15 0.91 0.05
t-test	0.3098			0.0588		

P-Value is non significant (P>0.05)

Table (10): Optical density value relative to mucopolysaccharides (PAS); alkaline and acid phosphates; and succinic dehydrogenase enzymes in livers of experimental groups after 24 hr. of anaesthesia.

		Control	Sevoflurane	Isoflurane
PAS	Mean	0.24	0.21	0.15
	S. D	0.03	0.04	0.03
	t-test		0.0001 *	
Alkaline Phosphates	Mean	0.63	0.60	0.64
	S. D	0.12	0.11	0.13
	t-test		0.197 $	
Acid Phosphates	Mean	1.34	1.35	1.31
	S. D	0.13	0.13	0.27
	T-test		0.5425 $	
Succinic Dehydrogenase	Mean	1.07	0.93	0.62
	S. D	0.14	0.12	0.10
	t-test		0.0001 *	

* P-Value is significant at <0.05

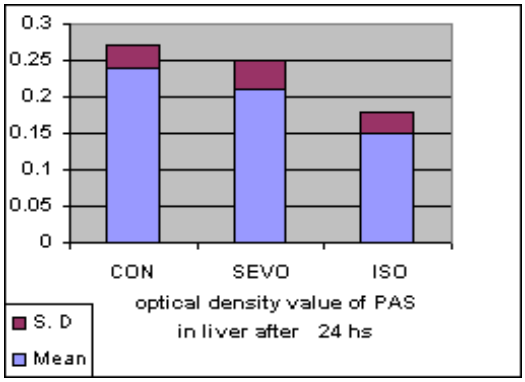
$ P-Value is non-significant at >0.05

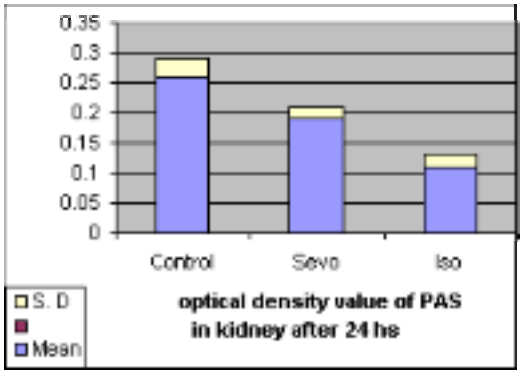
Table (11): Optical density value relative to mucopolysaccharides (PAS); alkaline and acid phosphates; and succinic dehydrogenase enzymes in Kidneys of experimental groups after 24 hr. of anaesthesia.

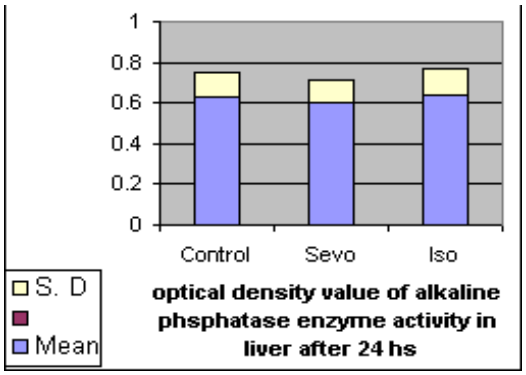
		Control	Sevoflurane	Isoflurane
PAS	Mean	0.26	0.19	0.11
	S. D	0.03	0.02	0.02
	t-test		0.0001 *	
Alkaline Phosphates	Mean	0.83	0.84	0.86
	S. D	0.17	0.12	0.13
	t-test		0.4376 $	
Acid Phosphates	Mean	1.42	1.45	1.37
	S. D	0.15	0.17	0.3
	T-test		0.2312 $	
Succinic Dehydrogenase	Mean	0.91	0.83	0.59
	S. D	0.08	0.1	0.11
	t-test		0.0001 *	

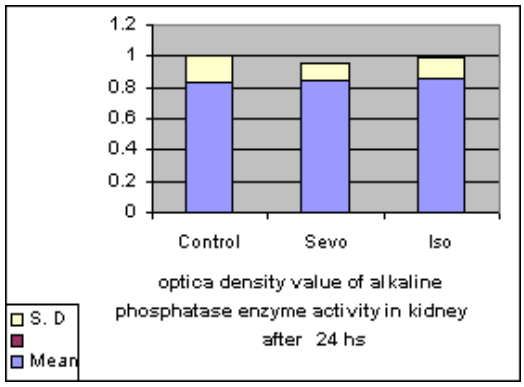
* P-Value is significant at <0.05

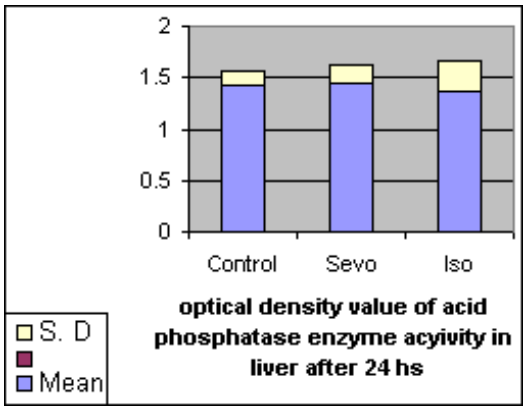
$ P-Value is non-significant at >0.05

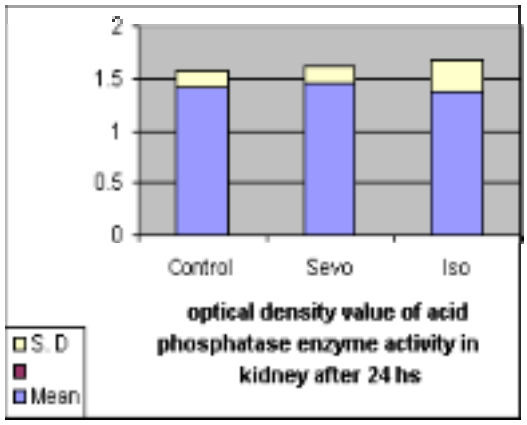


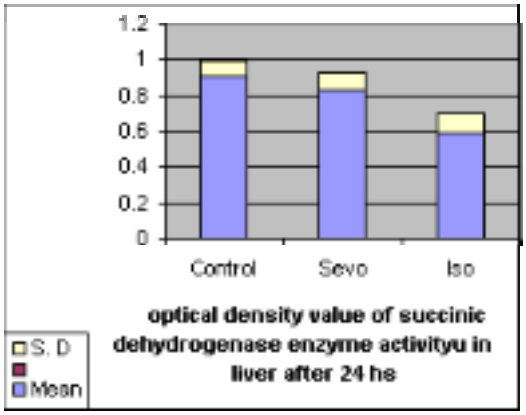


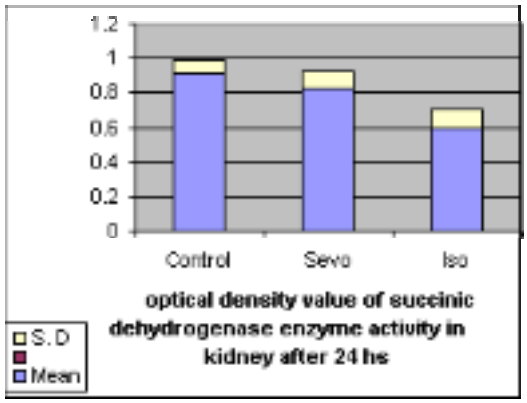












Discussion

The attributes of an inhalational anaesthetic that determine clinical usefulness include non-inflammability, rapid induction and emergence, as well as lack of effect on vital function during administration and absence of organ toxicity.

Pre-operative investigations of studied patient groups were within normal. While, intra-operative HR and BP of sevoflurane group showed non-significant reduction in heart rate and blood pressure, and normal electroca – rdiograms in comparison to pre-

operative investigations. Intra-operative investigations of isoflurane group showed significant increase in HR, BP (in 1st 30 minutes) and normal electro - cardiograms in comparison to pre-operative investigations and sevoflurane group.

Post-operative liver and kidney function tests of patients exposed to sevoflurane and isoflurane groups showed no significant difference. While, post-operative urine analysis showed (30mg/dl) albumin after 24 hr. of operation in isoflurane group in comparison to pre-operative investig - ation and sevoflurane group which were normal in urine analysis.

Frink et al. (1992) studied the effect of sevoflurane and isoflurane in patients during the period of operation and reported that, the administration of 0.5 MAC sevoflurane has been associated with stable and even a slight decrease in cardiac output, HR and BP than isoflurane, in which they were elevated. Ebert et al. (1995), reported the same effect and they added that, sevoflurane does not cause sympathetic nervous system activation or increase in heart rate and blood pressure. Inada et al. (1997) concluded that, sevoflurane increased the cardiac filling pressure, so, it decreased the HR and BP. While, Malan et al. (1995) reported that, sevoflurane was associated with syst - emic vascular resistance, which incre - ased the BP and HR, but there was no adverse effect on rhythmic stability of the cardiac muscle. In agreement with these results, Forrest (1983) and Rodrigo et al. (1986) reported that, isoflurane significantly increased the HR and cardiac out put but has no effect on rhythm stability of cardiac muscle.

In this study there was no change in O2 blood saturation or in End-tidal Co2. Ishibe et al. (1993) and Green, (1995) suggested that such an effect could be due to sevoflurane and isoflurane inhibition of the hypoxic pulmonary vasoconstriction, in which blood is diverted from poorly ventilated area to better ventilated area to maintain the arterial oxygen tension and reduction of CO2.

The present study demonstrated that sevoflurane and isoflurane had no significant mal effect on the liver and kidney function tests.Gelman et al. (1984) and Frink et al. (1992) reported that, isoflurane had an impact on hepatocellular function through reduction of oxygen and portal blood flow, but maintained hepatic arterial blood flow or increased it over un-anaesthetised value despite decreasing cardiac output. Targ et al. (1989) and Kharsch (1995) suggested that the low potential hepatic and renal toxicity of these drugs is due to their low blood solubility, great molecular stability and minimal insignificant biotransformation of isoflurane and sevoflurane in the body, ensure rapid clearance of each them at the end of anaesthesia. Ebert et al. (1998) used sensitive markers of renal tubular injury such as increased urinary excretion of glucose, protein and the proximal tubular enzymes. They found that there was no significant change in the average value of urinary glucose and protein concentration after 8 hours of operations with sevoflurane anaesthesia. Bito and Ikeda (1996) in a study performed on 10 surgical patients receiving sevoflurane for more than 10 hours, they found no change in renal function tests. On the other hand, Patel and Goa (1996), reported slight decrease in postoperative serum creatinin level with sevoflurane and isoflurane anaesthetic patients.

Liver function testes of experi - mental rats showed no significant difference in serum SGOT, SGPT, levels between control and treated

groups, after 24 hours and 7 days of sevoflurane and isoflurane anaesthesia. Eger (1984), reported an increase in liver enzymes after repeated exposures to isoflurane. Strum et al. (1987) reported that, 1MAC of sevoflurane has no toxic effect on liver. While, Soma et al. (1995) studied the effect of multiple administration of sevoflurane for 1 week to cynomolgus monkeys and found that, the enzyme concentrations (ALT, AST, LDH; CK) were significantly increased than the base line concentrations for different sevoflurane concentrations (1, 1.6 and 2MAC). All the increased liver enzymes of 1 MAC returned to normal at the end of 2nd week.

Histological examination of liver sections from sevoflurane treated group after 24 hours of anaesthesia showed normal hepatocytes and mild congestion in blood sinusoids and central veins. After 7 days of recovery, there was no histological change in liver sections. While, liver sections of isoflurane treated group after 24 hours of anaesthesia, showed hypochromic stained hepatocytes, cellular infiltration and congestion in blood sinusoids and around central veins. After 7 days, mild cellular infiltration and congested blood vessels were still present.

Study of direct sevoflurane and isoflurane exposure on guinea pig liver slices by Ghantous et al. (1992) showed no toxic effect on liver cells. Although, sevoflurane and isoflurane were readily biotransformed by liver slices, but their metabolites had low toxic potential effect. Also, Soma et al. (1995) reported that, multiple administration of 1 MAC sevoflurane to cynomolgus monkey (3 hours/day, 3days/week for 8 weeks) had no gross histopathological changes in liver. While, Bernard et al. (1992), reported liver congestion's and cellular infiltration in chronically treated dogs with sevoflurane and isoflurane. Frink (1995) reported cellular infiltration in liver sections in rats of isoflurane groups than sevoflurane group. He explained his results as due to biotr - ansformation of isoflurane to trifluoro-acetic acid (TFA), which may initiate immune response. On the other hand the organic metabolite of sevoflurane, hexafluoro isopropanol (HFIP) has much less protein binding capability than TFA. Also, the HFIP undergoes biotransformation to HFIP-glucuronide compound, which is rapidly excreted in urine within 12 hours.

Kidney function tests of experimental rats showed no significant difference in blood urea and serum creatinine levels between control and treated groups, after 24 hours and 7 days of anesthesia. Luu et al. (1985) reported minimal renal function changes after isoflurane anaesthesia due to reduction in renal blood flow, but return to baseline by the 1st post-operative day. Strum et al. (1987) reported that, 1 MAC of sevoflurane had no toxic effect on kidney. Histological examination of kidney sections in sevoflurane treated group, after 24 hours and 7 days of anaesthesia showed normal renal corpuscles and tubules. While, kidney sections of isoflurane treated group after 24 hours of anaesthesia, showed congestion and cellular infiltration between the renal tubules. There was no change after 7 days of anaesthesia. Plummer et al. (1986) stated that, isoflurane decreased the renal blood flow, but had no effect on rat kidney tissue. Also, Soma et al. (1995) stated that, multiple administrations of sevofl - urane to cynomolgus monkey had no histological changes in renal cortex or medulla.

Histochemical results of liver and kidney sections after 24 hours of sevoflurane and isoflurane anaesthesia

showed, significant decrease in optical density of PAS positive material and succinic dehydrogenase enzyme activity than control group. While, acid and alkaline phosphates enzymes activity showed no significant change. After 7 days of anaesthesia there was no change in optical density. Lunam et al. (1985) and Frink et al. (1995) stated that, the change in enzyme activity after anaesthesia might be due to a decrease of blood flow, and consequently decreased oxygen tension, which affects the extent of cellular activity rather than cellular damage. Also, they added that, the decrease in succinic dehydrogenase enzyme activity is due to decrease in oxidative respiration via the kreb's cycle in the cells. While, Massion et al. (1984) and Egar and Johnson (1987) suggested that exposure to 40% oxygen tension may also result in release of toxic free radicals that cause partial mitochondrial destruction and decrease in succinic dehydrogenase enzyme activity. Soma et al. (1995), Lochhead et al. (1997) and Arzac et al. (1998) reported that, non-significant change in enzyme activity in liver and kidney indicates that, there is no cellular damage in the hepatocytes and renal tubules.

Conclusion: from the previous histolo - gical, histochemical and clinical study we can conclude that sevoflurane has no harmful effect as an anaesthetic drug.

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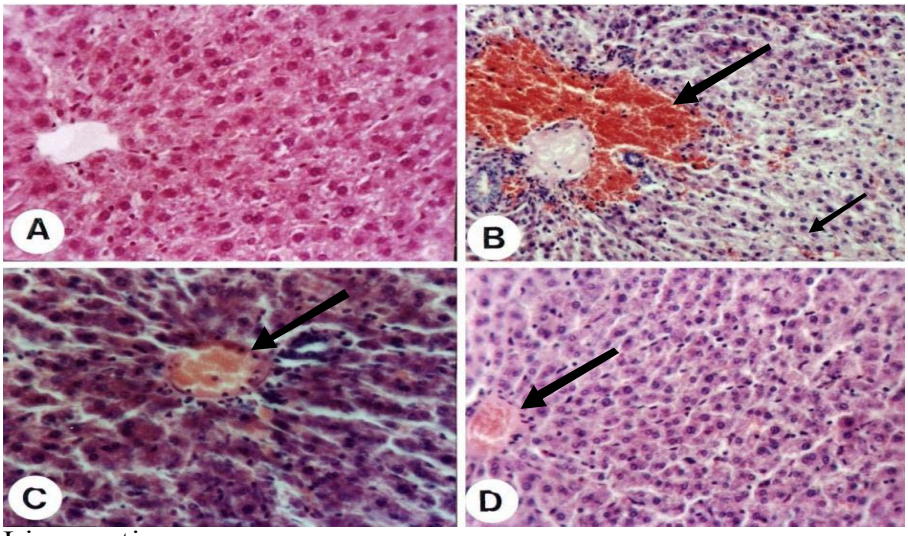

Fig. (1) Liver sections:
(A) 24 hours after exposure to isoflurane showing hyperemia, congested blood sinusoids, cellular infiltration and hypochromic stained hepatocytes.
(B) Control liver
(C) 24 hours after exposure to sevoflurane showing mild congestion in blood sinusoids and central vein.
(D)7 days after exposure to isoflurane showing congested blood vessels.
(HEX & E X 400)

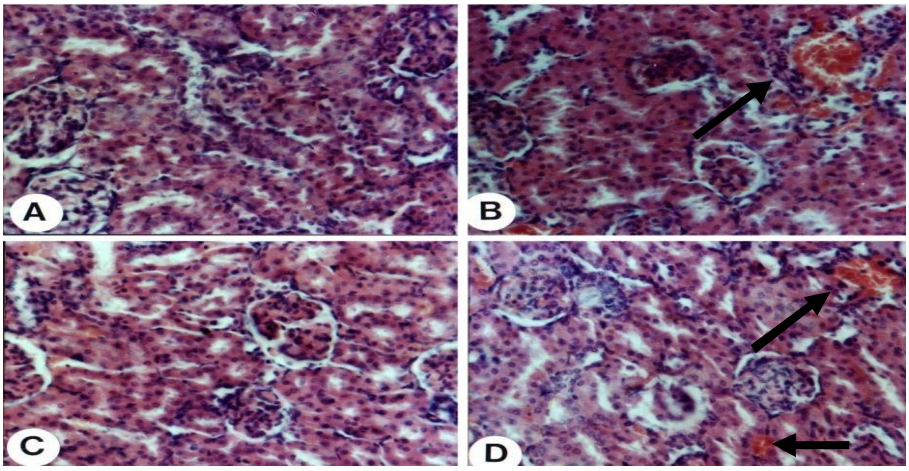

Fig. (2) Kidney sections:
(A) Control kidney.
(B) 24 hours after exposure to isoflurane showing hyperemia and cellular infiltration.
(C) 24 hours after exposure to sevoflurane showing mild congestion .
(D) 7days after exposure to isoflurane showing hyperemia.

(HX & E X 400)

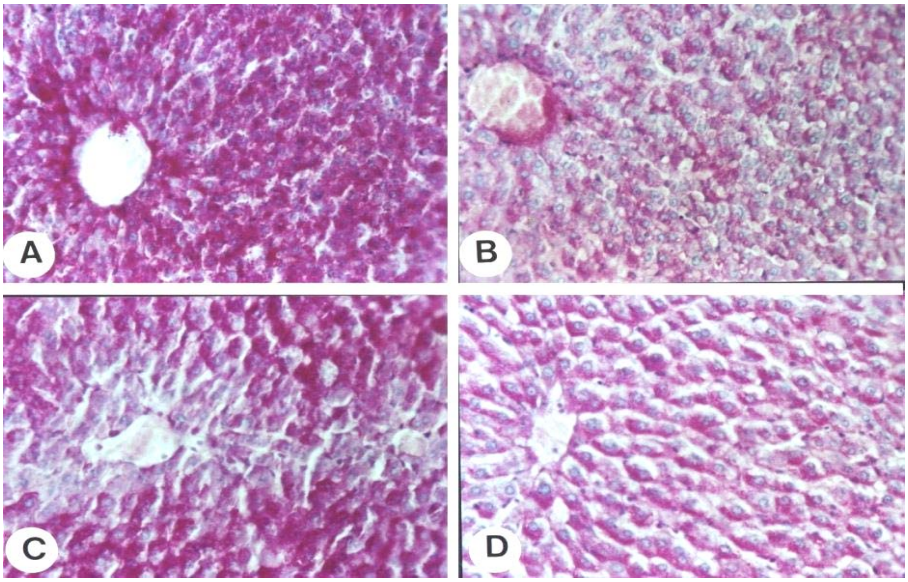

Fig. (3) Liver sections showing PAS positive material in hepatocytes:
(A) Control liver.
(B) 24 hours after exposure to isoflurane.
(C) 24 hours after exposure to sevoflurane.
(D)7days after exposure to isoflurane

(PAS X400)

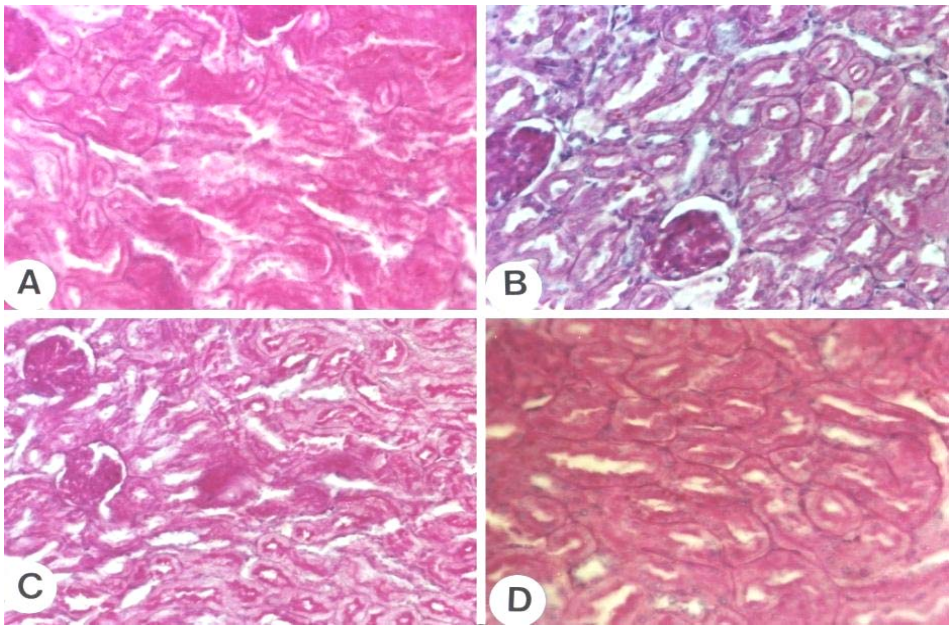

Fig. (4) Kidney sections showing PAS positive material in renal corpuscles and tubules:
(A) Control kidney.
(B) 24 hours after exposure to isoflurane.
(C) 24 hours after exposure to sevoflurane.
(D) 7days after exposure to isoflurane

(PAS X 400)

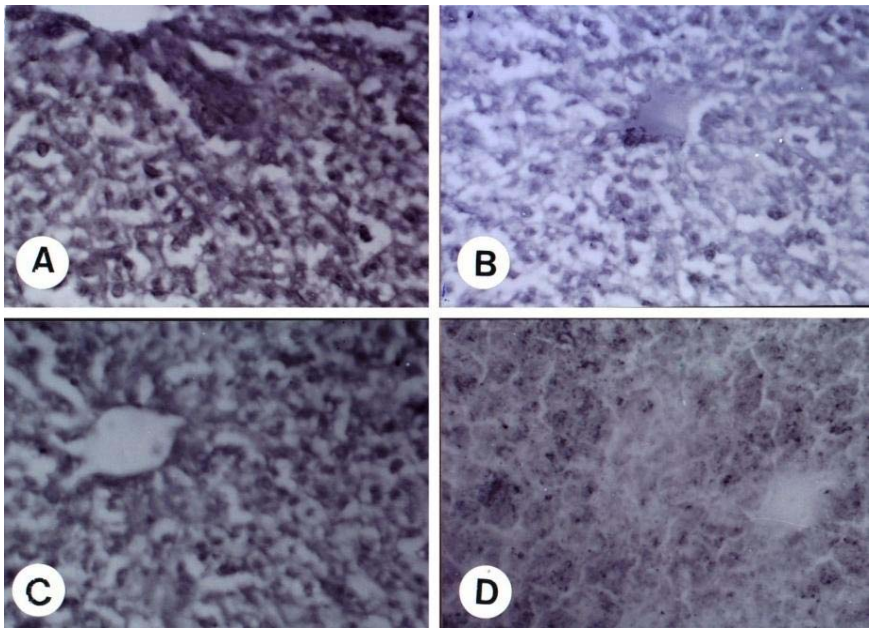

Fig. (5) Liver sections showing alkaline phosphatase enzyme activity in hepatocytes:
(A) Control liver
(B) 24 hours after exposure to isoflurane.
(C) 24 hours after exposure to sevoflurane.
(D)7days after exposure to isoflurane
(Gomori method X 400)

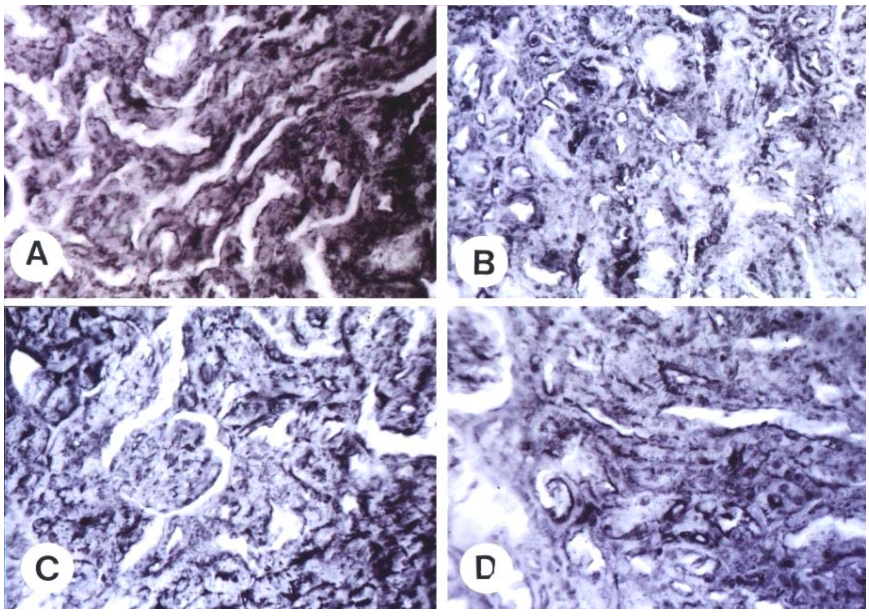

Fig. (6) Kidney sections showing alkaline phosphatase enzyme activity in renal corpuscles and tubules:
(A) Control kidney.
(C) 24 hours after exposure to sevoflurane.
(D) 7days after exposure to isoflurane
(Gomori method X 400)

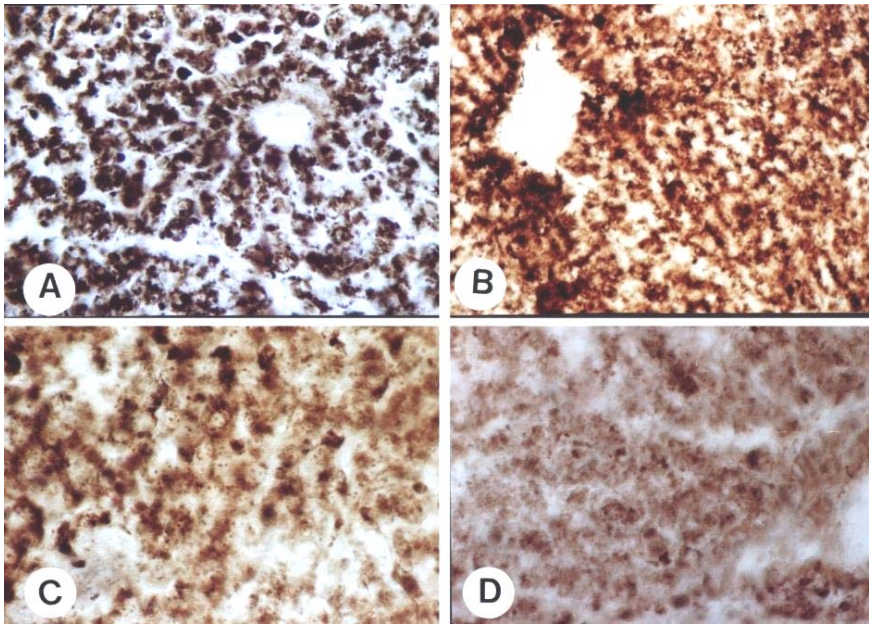

Fig. (7) Liver sections showing acid phosphatase enzyme activity in hepatocytes:
(A) Control liver
(B) 24 hours after exposure to isoflurane.
(C) 24 hours after exposure to sevoflurane.
(D) 7days after exposure to isoflurane
(Gomori method X 400)

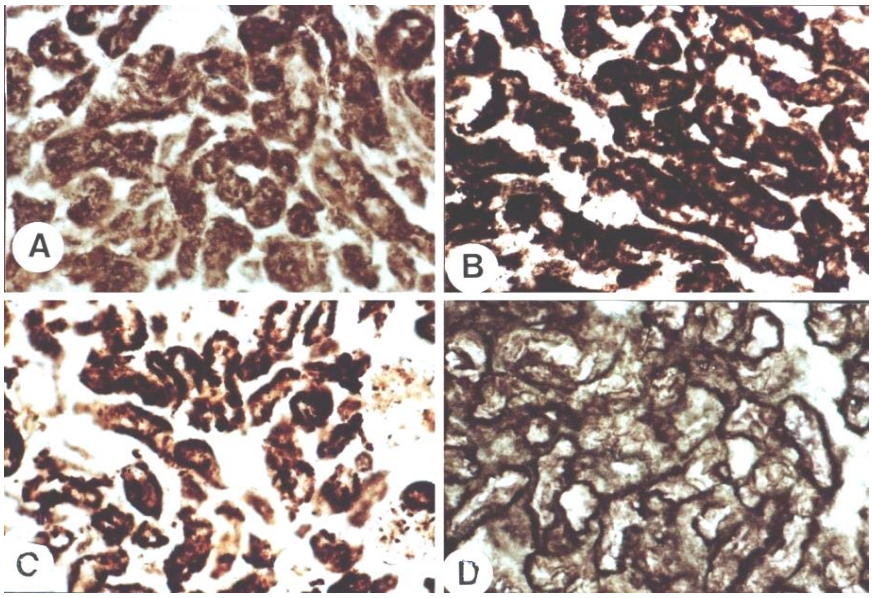

Fig. (8) Kidney sections showing acid phosphatase enzyme activity in renal corpuscles and tubules:
(A) Control kidney.
(B) 24 hours after exposure to isoflurane.
(C) 24 hours after exposure to sevoflurane.
(D) 7days after exposure to isoflurane
(Gomori method X 400)

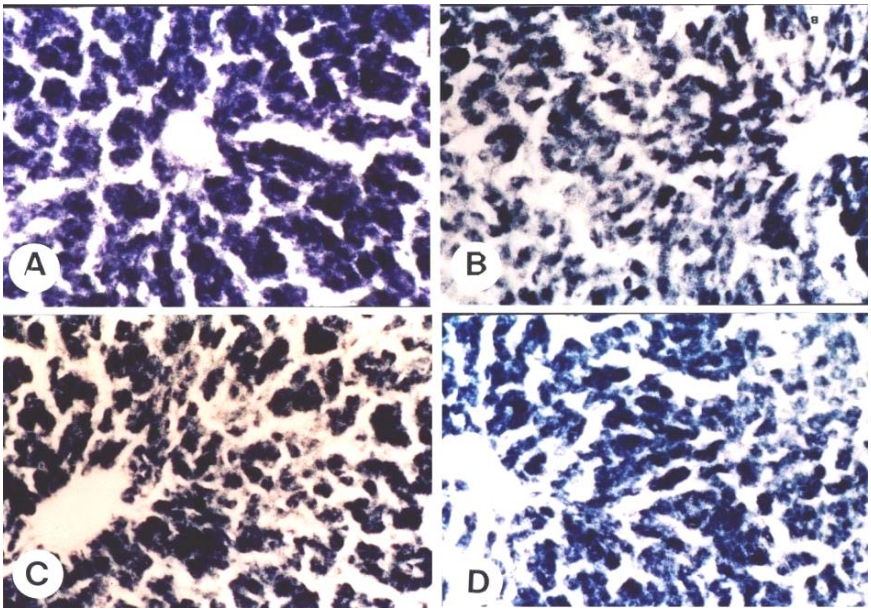

Fig. (9) Liver sections showing succinic dehydrogenase enzyme activity in hepatocytes:
(A) Control liver
(B) 24 hours after exposure to isoflurane.
(C) 24 hours after exposure to sevoflurane.
(D) 7days after exposure to isoflurane
(Nitro blue tetrazolium X 400)

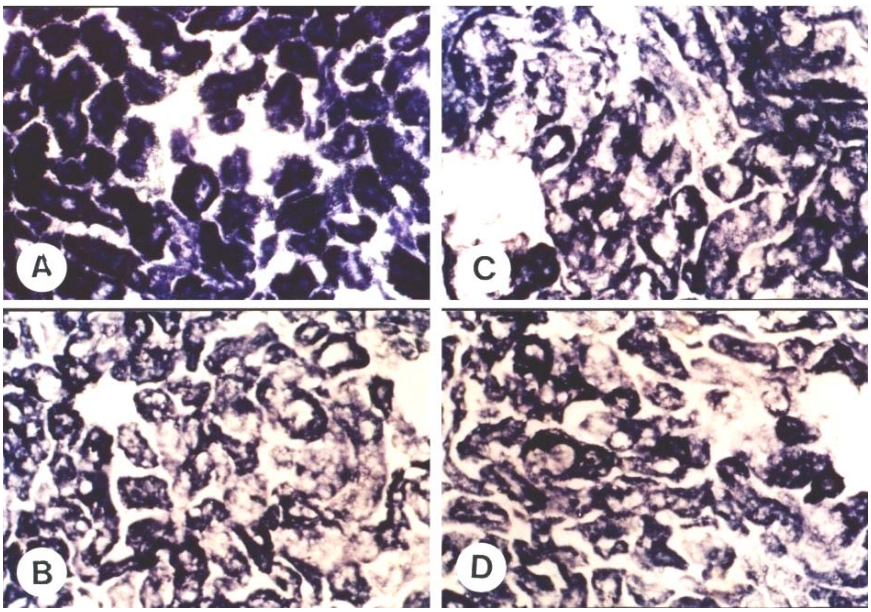

Fig. (10) Kidney sections showing succinic dehydrogenase enzyme activity in renal corpuscles and tubules:
(A) Control kidney.
(B) 24 hours after exposure to isoflurane.
(C) 24 hours after exposure to sevoflurane.
(D) 7days after exposure to isoflurane
(Nitro blue tetrazolium X 400)

دراسة هستولوجيه وأكلينيكيه مقارنه لعقارين للتخدير الاستنشاقي

محمود أحمد عبد الحليم مسعود * نصر الدين محمد صيام* * -كرم مرسى الروبى **
و عماد محمد أبو الفتوح**
أقسام الهستولوجى* و التخدير** و العناية المركزة**
كليه الطب جامعه الأزهر

يعتبر السيفوفلورين (فلوروميثيل 1,1,1,3,3,3سداسى فلورو ايزوبروبيل الأثير) واحد من المخدرات الأستنشاقيه المستخدمة حديثا، كما انه قوى وسريع التأثير، و يتحول إلى مواد غير سامه و سريع الخروج من الجسم، حيث يقترب حاجز الغاز و الدم له إلى حاجز الغاز و الدم المماثل لأكسيد النيتروز(6و. -7و.). و يزداد الاهتمام بالسيفوفلورين لأهميته في الجراحات السريعة و كذلك لقله رائحة الأثير به و ذوبانه السريع في الدم و الدهون والأنسجة.

صممت هذه الدراسة للمقارنه بين السيفوفلورين كمخدر حديث و الأيزوفلورين كمخدر مشهور من حيث تأثيره على ديناميكية الدم و الكبد و الكلى. تمت الدراسة الأكلينيكيه على 80 شخص بالغ من الجنسين أثناء أجراء عمليات جراحية لهم، و قسموا إلي مجموعتين، 40 شخص لكل مجموعه. خدرت المجموعة الأولى بالسيفوفلورين و خدرت المجموعة الثانية بالأيزوفلورين. تم عمل الفحوصات التقليدية ووظائف الكبد والكلى قبل العمليات وبعدها بساعتين و4ساعات و24ساعة و7 أيام من الإفاقة.

تمت الدراسة التجريبية علي .9 فأر أبيض من الجنسين، قسموا إلى 3 مجموعات، .3 فأر لكل مجموعة. المجموعة الأولى كمجموعة ضابطة و المجموعة الثانية خدرت بالسيفوفلورين و المجموعة الثالثة خدرت بالأيزوفلورين، تم تقسيم كل مجموعه إلى مجموعتين فرعيتين، 15 فأر بكل مجموعة، ذبحت المجموعة الأولى بعد 24 ساعة، والأخرى بعد 7 أيام من بداية التجربة. تم عمل وظائف الكبد والكلى قبل التخدير وبعد 24 ساعة من الأفاقة للمجموعه الأولى و بعد 7ايام للمجموعه الثانية. كما أخذت عينات

من أكباد و كلى الفئران لتحضيرها و صـبغها هسـتولوجيا وهسـتوكيميائيا لدراسـتها بالميكروسكوب الضوئي

أوضحت الدراسة الإكلينيكية أن متوسط دقات القلـب و ضـغط الـدم فـي مجموعـه السيفوفلورين كانت(ذات دلاله إحصائية) أقل منها في الأيزوفلورين وذلك أثناء العمليات، بينما لم يظهر أي تغير ذي دلاله أحصائيه في نمط موجات الرسام الكهربائي للقلب أثناء العمليات أو بعدها، وكذلك في وظائف الكبد أو الكلى أو نسبه التشبع بالأكسجين و مستوى ثاني أكسيد الكربون في الدم بعد العمليات. كما أوضحت الدراسة التجريبية أن عقـاري السيفوفلورين و الايزوفلورين ليس لهما تأثير ذو دلاله احصائيه على وظـائف الكبـد أو الكلى بعد العمليات. وقد أوضحت نتائج فحص الأنسجة في مجموعه السـيفوفلورين أن هناك احتقان بسيط بالأوعية الدموية لكبد المجموعة التي تم ذبحها بعد 24 ساعة واختفت في المجموعة التي تم ذبحها بعد 7 أيام، بينما زاد الاحتقان وظهرت خلايا ألتهابيه في كبد مجموعه الأيزوفلورين التي تم ذبحها بعد 24 ساعة ولم تختفى في المجموعة التـي تـم ذبحها بعد 7 أيام. كما أوضحت نتائج فحص أنسجة الكلى عدم وجـود تغيـرات فـي مجموعه السيفوفلورين، بينما ظهر احتقان و خلايا ألتهابيه في كلى مجموعه الأيزوفلورين التي تم ذبحهما بعد 24 ساعة، و اختفت في المجموعة التي تم ذبحها بعد 7 أيام. وقـد أظهرت الدر اسه الهيستوكيميائيه لنسيج الكبد و الكلى أن هناك نقص ذو دلاله أحصائيه في صبغه البرأيودك اسيد اتشيف و نشاط إنزيم السكسينيك دى هيدروجيناز خاصة فـي مجموعه الأيزوفلورين مقارنه بمجموعه السيفوفلورين وذلك في المجموعة التي تم ذبحها بعد 24 ساعة، بينما لم يظهر تغير في المجموعة التي تم ذبحها بعد 7 أيام. كما لم يوجد تغير ذو دلاله أحصائيه في أنزيم الفوسفاتيز القلوي أو الحامضى في كل من المجموعتين. و من خلال الدراسة الهيستولوجيه و الهيستوكيميائيه و الأكلينيكيه. نستخلص أن عقـار السيفوفلورين ليس له تأثير ضار و أنه مخدر استنشاقي آمن.