ASSESSMENT OF HEPATIC, RESPIRATORY AND METABOLIC DERANGEMENTS IN PATIENTS DURING AND AFTER ISOFLURANE ANESTHESIA IN SURGICAL OPERATIONS

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ABSTRACT

Worldwide, general anesthetics and sedatives are used in hundreds of thousands of patients every year during surgical operations, invasive procedures, and imaging studies. Isoflurane is the commonest inhalational anesthetic used nowadays. This study was conducted to evaluate the respiratory , metabolic and hepatic impacts of isoflurane exposure by biochemical assays to estimate respiratory and metabolic parameters (pH, Pco_2, Po_2, bicarbonate, glucose and lactate) and liver function tests (AST, ALT and Alpha-GST). The current study was carried out on apparently healthy 40 male and female patients who were classified into two major groups; Group I (control) and Group II who exposed to isoflurane anesthetic for 4 hours during vitrectomy operation in ophthalmic operation theatre, Kasr El Aini Hospital. Arterial and venous blood samples were taken at 1, 2,3 and 4 h time points during isoflurane exposure and at 1, 2,3 and 4 h time points after discontinuation of isoflurane to assess respiratory and metabolic parameters (pH, Pco_2 and Po_2, bicarbonate, glucose and Lactate) in addition to liver function tests (AST, ALT and Alpha-GST). Isoflurane exposure led to respiratory and metabolic derangements in group II. There was significant reduction in pH, bicarbonate and blood glucose level with significant elevation in lactate and $PaCo_2$ through the 2^{nd} hour, 3^{rd} hour and 4^{th} hour during exposure time. After cessation of isoflurane, metabolic markers gradually normalized in group II. PaO_2 was stable in both groups with no significant changes as both groups were oxygenated. As regard liver function tests, significant elevation in serum level of AST, ALT and Alpha-GST were recorded in group II through the 3^{rd} hour and 4^{th} hour during exposure time. Gradual decrease of their levels through the 3^{rd} hour and 4^{th} hour during post operative period was noticed. The previously declared results revealed that isoflurane possess hazardous effects on general health. It causes liver, metabolic and respiratory dysfunction. Thus repeated anesthesia within a short period of time should be approached with caution since the risk of hepatotoxicity, metabolic and respiratory dysfunction is suspected.

Key-words: *Isoflurane, Anesthetic, Hepatic, Respiratory and Metabolic Toxicity.*

INTRODUCTION

Anesthesia is a pharmacologically induced reversible state of amnesia, analgesia, loss of responsiveness, loss of skeletal muscle reflexes or decreased stress re-

sponse, or all simultaneously. This allows patients to undergo surgery and other procedures without the distress and pain they would otherwise experience. General anesthesia refers to inhibition of sensory, motor and sympathetic nerve transmission at the level of the brain, resulting in unconsciousness and lack of sensation (Brill et al., 2003).

Ioflurane(2-chloro-2-(difluoromethoxy)-1,1,1-trifluoro-ethane) is a halogenated ether used for inhalational anesthesia. Isoflurane reduces pain sensitivity (analgesia) and relaxes muscles. The mechanism by which general anesthetics produce the anesthetic state is not clearly understood, but likely involves interactions with multiple receptor sites to interfere with synaptic transmission. Isoflurane binds to GABA receptors, glutamate receptors and glycine receptors, and also inhibits conduction in activated potassium channels (Jevtovic-Todorovic et al., 2003).

It is well known that halogenated ether anesthesia are dose dependent respiratory depressants (Lu et al., 2006). Concerns have been raised as to the safety of certain general anesthetics, in particular ketamine and isoflurane in neonates and young children due to their susceptible respiratory depressive effects. This has led to the FDA and other bodies to take steps to investigate these concerns (Mellon et al., 2007).

Hypoglycemia has been defined as blood glucose less than 40 mg/dL, (Ogata, 1999) 45 mg/dL, (WHO, 1997) or, 60 mg/dL (Stanley & Baker, 1999). Hypoglycemia during inhaled anesthesia in mice has been reported previously, as blood glucose level decreased to less than 20 mg/dL. Severe hypoglycemia has been shown to cause neuronal apoptosis and necrosis in many animal models (Ouyang et al., 2000 & Auer, 2004).

Acidosis is an increased acidity in the blood, which occurs when arterial pH falls below 7.35. Lactic acid is produced in the body when oxygen levels drop. Lactic acidosis is the term used when lactic acid is built up in the bloodstream faster than it can be expelled (John, 2000). A commonly reported side effect of volatile anesthesia in mice is disturbance of the acid-base balance, e.g., acidosis (Szczesny et al., 2004 and Henriksna et al., 2005).

Since starting to use sevoflurane and isoflurane, Nishiyama et al. (1998) have questioned their effects on liver function because abnormal serum concentrations of liver enzymes seemed to be increased compared to those observed after enflurance anesthesia. Some studies have compared liver functions after sevoflurane and isoflurane anesthesia and after halothane anesthesia. Although both sevoflurane and isoflurane are less hepatoxic than halothane, recently some cases of liver dys-

function have been reported after sevoflurane anesthesia.

As with all halogenated anesthetics, repeat anesthesia within a short period of time should be approached with caution since the risk of hepatotoxicity is suspected. There is insufficient experience of use in repeated anesthesia to make a definite recommendation in this regard. Caution should be exercised with administering isoflurane to patients with pre-existing liver disease (Schmidt et al., 1999).

Glutathione S-transferases are a family of enzymes involved in the binding, transport, and detoxification of a wide variety of endogenous and exogenous compounds (Mulder et al., 1999). Alpha-Glutathione S-transferase (alpha-GST) has been advocated as a better marker of hepatocellular damage than the transaminases in toxic and autoimmune hepatitis (Mazur et al., 2003). It is a cytosolic enzyme predominantly located in hepatocytes with a uniform distribution in the liver. Several clinical and experimental studies have shown that alpha-GST is an early and sensitive parameter for hepatocellular membrane damage (Kobayashi et al., 2000).

AIM OF THE WORK

This study was conducted to evaluate the respiratory metabolic and hepatic impacts of isoflurane exposure by biochemical assays to estimate respiratory and metabolic parameters (pH, Pco_2, Po_2, bicarbonate, glucose and lactate) and liver function tests (AST,ALT and alpha- GST).

SUBJECTS & METHODS

Subjects: The current study was carried out on apparently healthy 40 male and female adults (aged between 20-40 years) with the following exclusion criteria:

- Patients with known respiratory disorders.
- Patients with known metabolic disorders.
- Patients with known hepatic disorders.
- Operative time more or less than 4 hours.

Subjects were classified into two major groups:

Group I (control): this group included 10 control adult male and female patients who were fasted for 16 hours (supposed 8 hours for preoperative fasting period + supposed 4 hours operative time + supposed 4 hours postoperative time during this period patients breath oxygen by face mask to simulate the same intraoperative and postoperative oxygenation) in ophthalmic ward.

Group II (Isoflurane): this group included 30 adult male and female patients

exposed to isoflurane anesthesia for 4 hours during vitrectomy surgery (vitreous eye surgery) in ophthalmic operation theatre in Kasr El Aini Hospital. Patients were fasted for 16 hours (8 hours preoperative fasting period+ 4 hours operative time + 4 hours fasting until oral feeding is resumed after surgery). Patients transferred to post anesthesia care unit (PACU) to spend the 4 postoperative hours during this period patients breathe oxygen by face mask. All patients in both groups (I & II) were hydrated by IV physiologic ringer solution 10 ml/kg/4 hours during the 16 hours of the total oral fasting period. This hydration was decided to prevent dehydration and hemo-concentration which may give false laboratory metabolic results and may insult the patient general health condition (Yogendran et al., 1995).

METHODS:

I. Informed consent:

Prior to their inclusion in this study, all patients signed informed consent.

II. Isoflurane Treatment:

Before starting any operation intensive care unit was booked for any susceptibility of respiratory depression

Group II: after 8 hours fasting and with no premedication drugs that may interfere with our results, anesthesia was induced using IV propofol 2mg/kg. Airway is secured and breathing is maintained throughout surgery by laryngeal mask airway (LMA) which is a device replacing the endotrachial tube and allow spontaneous breathing during anesthesia (Ashworth and Smith, 1998). Anesthesia is maintained using isoflurane with concentration dose between 2-4% according to the dose that prevents spontaneous movement denoting adequate anesthesia and analgesia for the patient. Anesthesia machine delivered isoflurane in combination with O_2 60% (Topal et al., 2003).

Radial arterial catheter was inserted to every patient by complete sterile technique and repeated flushing with heparinated saline to ensure patency of the catheter for arterial sampling for arterial blood gases (ABG), PH, bicarbonate, glucose and lactate. Samples were taken every hour for 8 hours (4 intraoperative hours + 4 postoperative hours). Venous canulla was inserted at the dorsum of the hand. Venous blood samples were taken for alpha-GST, ALT & AST levels every hour for 8 hours (4 intraoperative hours + 4 postoperative hours) (Tiainen and Rosenberg, 1996).

IV. Metabolic parameters:

Arterial blood was aspirated at 1, 2, 3 and 4 h time points during isoflurane exposure (during the operation) in group II and during the parallel supposed 4 hour time in group I and at 1, 2, 3 and 4 h time points after discontinuation of isoflurane (after cessation of the operation), in group II and during the parallel supposed 4 hour

time in group I to assess:

- PH, Pco_2, Po_2, bicarbonate and lactate: are performed by gem premiere 3000 blood gas 2010 (Instrumentation Laboratory, USA) (Steinfelder-Visscher et al., 2006).
- Blood glucose: Blood glucose estimation by glucose oxidase method using automated chemistry analyzer (Dimension® RxL Max® Integrated Chemistry System- Siemens Healthcare Diagnostics, US (Trinder, 1969).
- Liver function tests: Aspartate and alanine transaminase (AST and ALT) activities were determined according to the method of Reitman and Frankel (1957). Alpha-Glutathione S-transferases (alpha-GST) concentration was measured with a time resolved immunofluorometric assay according to a standard assay procedure (Tiainen and Karhi, 1994).

Statistical Analysis:

All results are expressed as mean ± SD. Results were averaged before statistical analysis. Intergroup comparisons were evaluated using one-way analysis of variance for repeated measures; where indicated, Bonferroni's corrections were used to identify significant differences (Yosry and Othman, 2008).

RESULTS

Table (1) demonstrated that isoflurane exposure led to respiratory and metabolic derangements in group II. There was significant reduction in pH, bicarbonate (metabolic acidosis) and blood glucose level (hypoglycemia) with significant elevation in lactate and $PaCo_2$ (respiratory acidosis and respiratory depression) through the 2nd hour, 3rd hour & 4th hour during exposure time.

Table (2) showed that after cessation of isoflurane, metabolic parameters gradually normalized in group II. PaO_2 was stable in both groups with no significant changes as both groups were oxygenated.

As demonstrated in table (3), an elevation in serum level of AST, ALT and alpha-GST was recorded in group II that was significant versus control through the 3rd hour & 4th hour during isoflurane exposure time.

As demonstrated in table (4), an elevation in serum level of AST, ALT and alpha-GST was recorded in group II that was significant versus control through the 1st hour & 2nd hour during Post operative period with gradual decrease of their levels through the 3rd hour & 4th hour during Post operative period.

DISCUSSION

For inhaled anesthetics, isoflurane

and sevoflurane are frequently used. A commonly reported side effect of isoflurane anesthesia in mice is disturbance of the acid-base balance, e.g., acidosis (Henriksna et al., 2005). Metabolic acidosis may result from increased production of metabolic acids (lactic acid) or disturbances in the ability to excrete acid via the kidneys while respiratory acidosis results from a build-up of carbon dioxide in the blood (hypercapnia) due to hypoventilation and exposure to anaesthetics and sedatives (John, 2000). Also volatile anesthetics have been shown to produce respiratory depression in immature animals.

In the current study, isoflurane exposure led to respiratory and metabolic derangements in anesthetized patients (group II). There was significant reduction in pH, bicarbonate and blood glucose level with significant elevation in lactate and $PaCo_2$ which worsened with increased duration of isoflurane exposure (2nd hour, 3rd hour & 4th hour). After cessation of isoflurane, metabolic parameters gradually normalized in group II. PaO_2 was stable in both groups with no significant changes as both groups were oxygenated.

Similar results were previously reported by Loepke et al. (2009) who found that continuous respiratory acidosis, combined with a progressive metabolic acidosis and a decrease in blood glucose was observed in mice exposed to isoflurane anesthetic. Rozet et al. (2009) found that volatile anesthetics were associated with higher serum lactate, when compared with intravenous anesthetics. Similar values for pH and PCO_2 previously reported in isoflurane-anesthetized spontaneously breathing mice thus one can conclude that isoflurane anesthesia induces acidosis (Sjöblom and Nylander, 2007).

Topal and Gül (2006) found that respiratory depressant effects of isoflurane is characterised by increased $PaCO_2$ and decreased blood pH values thus arterial $PaCO_2$ rose from 33.6 mmHg to a peak of 51.5 mmHg in the isoflurane anesthetized patients.

Moreover, metabolic lactacidosis and hypoglycemia worsened with increased duration of isoflurane exposure, suggesting that prolonged isoflurane exposure was responsible for the metabolic derangement (Loepke et al., 2009).

Isoflurane seems to be better than sevoflurane because the former is less metabolized in the liver. However, previous studies found that isoflurane increased serum levels of liver enzymes more often than did sevoflurane in patients without preoperative liver dysfunction (Nishiyama et al., 1999). Isoflu-

rane and sevoflurane are not viewed as hepatotoxins. However, fulminant liver failure was reported after repeated isoflurane anesthesia (Brunt et al., 1991). Liver necrosis was also seen after isoflurane anesthesia (Weitz et al., 1997).

The activity of alpha-GST is reported to reflect interstitial liver damage better than that of aminotransferases, (Mazur et al., 2003). Alpha-GST may be a more sensitive indicator of hepatocellular damage because its distribution is correlated to the proportion of functioning liver tissue present. Sudden shift in concentration of alpha-GST may be a better predictor of impending hepatic dysfunction than conventional tests (Kobayashi et al., 2000).

The current results show that the levels of liver function tests (AST, ALT and alpha-GST) were significantly higher in group II (isoflurane exposed group) as compared to normal controls, which is consistent with results obtained by Nishiyama et al. (2004) who stated that liver enzymes such as ALT, AST and alkaline phosphatase increased significantly in the isoflurane exposed patients.

The factors that can induce liver damage after inhalation anesthesia may be; increased intracellular calcium concentration, metabolites of anesthetics, decreased hepatic blood flow during anesthesia and other drugs that may be administered intraopertively (Nishiyama et al., 1998).

Covalent binding to subcellular proteins by the trifluoroacetyl acid (TFA) chloride intermediate, a common metabolite of halothane and isoflurane generated by oxidative biotransformation by the cytochrome P450 in the liver, is implicated as a mechanism of centrilobular necrosis of the liver. In this respect, sevoflurane and desflurane, which do not have chloride, might be safer than other chlorinated anesthetics (Lind et al., 1990).

CONCLUSION AND RECOMMENDATIONS

The previously declared results revealed that isoflurane possess hazardous effects. It causes liver, metabolic and respiratory dysfunction. Thus repeated anesthesia within a short period of time should be approached with caution since the risk of hepatotoxicity, metabolic and respiratory dysfunction is suspected. Concurrent use of other respiratory depressants during surgical operation should be avoided with isoflurane anesthesia. Before starting any operation with isoflurane, intensive care unit should be booked for any susceptibility of respiratory depression.

Table 1: Respiratory and metabolic changes during Isoflurane exposure time in both groups.

	1st hour	2nd hour	3rd hour	4th hour
PaO_2 mmHg				
Group I	266.29 ±65.57	258.19 ±64.87	271.21 ±65.65	264.11 ±67.21
Group II	256.29 ±63.18	249.54±64.65	241.25 ±66.51	239.31±65.43
$PaCO_2$ mmHg				
Group I	36 ± 0.7	33 ± 0.6	32 ± 0.8	35.2 ± 0.6
Group II	37 ± 0.5	42 ± 0.9*	43 ± 0.8*	45.5 ± 1.7*
pH				
Group I	7.37 ± 0.04	7.39 ± 0.03	7.38 ± 0.04	7.4 ± 0.01
Group II	7.37 ± 0.05	7.31 ± 0.02*	7.30 ± 0.03*	7.28 ± 0.05*
Lactate µmol•1^{-1}				
Group I	1.1 ± 0.03	1 ± 0.02	1 ± 0.03	1 ± 0.02
Group II	1.2 ± 0.03	1.8 ± 0.03*	2 ± 0.03*	2.1 ± 0.02*
Bicarbonate mEq•1^{-1}				
Group I	25 ± 2	23 ± 3	25 ± 4	20 ± 2
Group II	21 ± 3	21 ± 2	15 ± 1*	13 ± 1*
Blood Glucose mg/dL				
Group I	110 ± 5	102± 4	98± 4	95± 3
Group II	113± 4	80± 3*	58± 2*	52± 3*

*$P < 0.05$ (group II *vs.* group I)

N=30 in group II & 10 in group I

Results are presented as mean ± SD.

PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide.

Table 2: Respiratory and metabolic changes during post operative period in both groups.

	1st hour	2nd hour	3rd hour	4th hour
PaO_2 mmHg				
Group I	243.15 ±63.57	256.53 ±65.52	241.72 ±64.94	261.29 ±65.25
Group II	236.34 ±66.63	256.61 ±65.13	261.27 ±65.41	266.62 ±64.57
$PaCO_2$ mmHg				
Group I	35 ± 0.8	33 ± 0.5	33 ± 0.7	35.2 ± 0.6
Group II	45 ± 0.5*	40 ± 0.9*	38 ± 0.8	36.5 ± 1.1
pH				
Group I	7.4 ± 0.03	7.39 ± 0.05	7.4 ± 0.02	7.39 ± 0.02
Group II	7.23 ± 0.05*	7.29 ± 0.03*	7.36 ± 0.08	7.38 ± 0.07
Lactate $\mu mol \cdot 1^{-1}$				
Group I	1.1 ± 0.03	1 ± 0.02	1 ± 0.03	1 ± 0.02
Group II	2.2 ± 0.03*	2.1 ± 0.06*	1.4 ± 0.03	1 ± 0.06
Bicarbonate $mEq \cdot 1^{-1}$				
Group I	21 ± 2	24 ± 3	28 ± 1	26 ± 3
Group II	13 ± 1*	18 ± 1	22 ± 2	25 ± 3
Blood Glucose mg/dL				
Group I	97± 4	99± 5	88± 3	85± 3
Group II	61± 2*	69± 2*	78± 4	81± 3

*$P < 0.05$, group II *vs.* group I.

N=30 in group II & 10 in group I.

Results are presented as mean ± SD.

PaO_2: partial pressure of oxygen; **$PaCO_2$**: partial pressure of carbon dioxide.

Table 3: Liver function parameters during Isoflurane exposure time in both groups.

	1st hour	2nd hour	3rd hour	4th hour
AST (U/l)				
Group I	**28.49**±2.3	**29.45**±1.9	**29.11**±2.9	**27.95**±2.4
Group II	32.76± 2.9	43.87 ± 3.5	55.65 ± 4.7*	62.22 ± 4.4*
ALT (U/l)				
Group I	**36.18**±2.4	**35.58**±3.4	**34.98**±3.8	**35.22**±2.9
Group II	37.99 ± 3.1	45 ± 4.1	59.46 ± 4.2*	69.47 ± 4.8*
GSTA (ug/l)				
Group I	1.6±0.05	1.7±0.09	1.6±0.07	1.8±0.09
Group II	1.9±0.06	3.2±0.10*	3.4±0.13*	3.9±0.17*

*$P < 0.05$, group II *vs.* group I.

N=30 in group II & 10 in group I.

Results are presented as mean ± SD.

Table 4: Liver function parameters during post operative period in both groups.

	1st hour	2nd hour	3rd hour	4th hour
AST (U/l)				
Group I	**27.89**±3.3	**29.29**±2.9	**28.49**±2.3	**27.69**±2.5
Group II	61.32 ± 4.5*	56.76 ± 4.7*	49.87 ± 3.9	39.31 ± 3.1
ALT (U/l)				
Group I	**35.88**±2.7	**36.12**±3.4	**34.78**±2.4	**37.18**±3.1
Group II	70.43 ± 6.2*	61 ± 5.2*	53.87 ± 4.5	43.51 ± 3.7
GSTA (ug/l)				
Group I	1.6±0.05	1.7±0.04	1.6±0.09	1.8±0.06
Group II	4.1±0.15*	3.8±0.12*	3.4±0.16*	2.9±0.12

*$P < 0.05$, group II *vs.* group I.

N=30 in group II & 10 in group I.

Results are presented as mean ± SD.

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تقييم التأثيرات الكبدية و التنفسية و الأيضية للمرضى أثناء وبعد التخدير بعقار الأيزوفلورين في العمليات الجراحية

المشتركون فى البحث

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في جميع أنحاء العالم ، يتم استخدام المسكنات والمهدئات في مئات الآلاف من المرضى في كل عام أثناء العمليات الجراحية ، و الإجراءات التداخلية المؤلمة ، ودراسات التصويربالأشعة.

و يعتبر الأيزوفلورين هو المخدر الأكثر شيوعا كمخدراستنشاقى في الوقت الحاضر. وقد أجريت هذه الدراسة لتقييم التأثيرات الكبدية و التنفسية و الأيضية جراء التخدير بعقار الأيزوفلورين بواسطة الفحوصات البيوكيميائية لتقدير الدلالات التنفسية و الأيضية (درجة الحموضة و ضغط الأكسجين و ضغط ثاني أكسيد الكربون، البيكربونات والجلوكوز واللاكتات) في الدم واختبارات وظائف الكبد من المرضى(الذكور و الإناث) الذين تم تصنيفهم في مجموعتين رئيسيتين ، 40 وقد أجريت الدراسة الحالية على (AST, ALT & GSTA) المجموعة الأولى (الضابطة) و المجموعة الثانية التي تتعرض لمخدر أيزوفلورين لمدة 4 ساعات خلال عملية استئصال الجسم الزجاجي في عمليات العيون في مستشفى قصر العينى. وقد أخذت عينات من الدم الشرياني والدم الوريدي بعد 1 و 2 و 3 و 4 ساعات خلال التعرض للأيزوفلورين وفي 1 و 2 و 3 و 4 ساعات بعد توقف الأيزوفلورين لتقييم المعايير التنفسية و الأيضية (درجة الحموضة و ضغط الأكسجين و ضغط ثاني أكسيد الكربون و البيكربونات و الجلوكوز واللاكتات) بالإضافة إلى اختبارات وظائف الكبد (AST, ALT & GSTA).

و قد أدى التعرض للأيزوفلورين إلي خلل في الدلالات التنفسية و الأيضية في المجموعة الثانية. فقد كان هناك إنخفاضاً ذو دلالة إحصائية في البيكربونات ، ودرجة الحموضة ومستوى السكر في الدم مع ارتفاع ذو دلالة إحصائية في اللاكتات و ضغط ثاني أكسيد الكربون خلال 2 و 3 و 4 ساعات في زمن التعرض. و بعد توقف أيزوفلورين قد تحسنت الدلالات التنفسية و الأيضية تدريجياً في المجموعة الثانية. وكان ضغط الأكسجين مستقراً في كل من المجموعتين مع عدم وجود تغييرات كبيرة نظراً لتعرض كلا المجموعتين إلي الأكسجين. و في اختبارات و ظائف الكبد ، تم تسجيل ارتفاع ذو دلالة إحصائية في مستوى (AST, ALT & GSTA) في المجموعة الثانية في مقابل المجموعة الضابطة في خلال 3 و 4 ساعات في زمن التعرض. وقد لوحظ انخفاض تدريجي في مستوياتها خلال 3 و 4 ساعات في فترة ما بعد الجراحة. و قد أظهرت النتائج ان التعرض للأيزوفلورين يملك تأثيرات خطيرة على الصحة العامة. فإنه يتسبب في أمراض الكبد ، و خلل في الوظائف التنفسية و الأيضية. ولذلك ينبغي الحذرعند التعرض للتخدير بعقار الأيزوفلورين في غضون فترات قصيرة حيث إنه يتسبب في أمراض الكبد ، و خلل في الوظائف التنفسية و الأيضية.