Effects of Halothane Anesthesia on Patients with Abnormal Renal Function Tests

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Abstract

Thirty patients (age range 10-70 years), (14) 46.7% males and 16 (53.3%) females, all of them presented with abnormal renal functions were studied in Basrah General Hospital during the period from (March to November 2007), for evaluate safety of halothane anesthesia during routine investigations to elective surgeries under general anaesthesia(the common use of halothane known to cause hepatotoxicity), In addition, drugs like analgesics and antibiotics are, also, heavily used particularly in the postoperative period. Several of these drugs can compromise renal functions, five milliliters from venous blood were taken before operation and then immediately after the operation, and on the first and third day postoperatively. Blood was tested for (blood urea nitrogen (BUN), serum creatinine and serum uric acid), using appropriate kits. Seventeenth (56.7%) had repeated exposure to halothane by underwent previous surgeries, and 13 (43.3%) are newly exposed to halothane. No significance change had been observed in relation to gender of patients for all parameters. We conclude that laboratory values immediately after surgical operations and for 3 days later have no trend for a major derangement in patients with renal diseases.

تأثير التخدير بالهالوثين على المرضى المصابين بأضطراب في وظائف الكليه

الخلاصة

اجريت الدراسة على(30) مريض مصاب باضطراب وظائف الكليه تتراوح اعمارهم (10- 70) سنه، (14) 46.7% منهم ذكور ، و (16) 53.3 % أناثا خلال الفترة من اذارالى تشرين الثاني 2007 في مستشفى البصرة العام ، أجريت الدراسه بصورة عشوائية لغرض تقدير السلامه وتقيم النتائج المختبريه.

هؤلاء المرضى تعرضوا للتخدير العام (الاستعمال الشائع للهالوثين المعروف بتسببه في سمية الكبد) ،باالاظافه الى بعض الادويه التي تستخدم بعد العمليه الجراحيه التي لها تاثير على وظائف الكليه، أخذت خمسة ملليلترات من الدم الوريدي قبل وبعد العملية، ومن ثم في اليوم الأول واليوم الثالث بعد العملية – وأختبر لتحديد مستويات اليوريا والكرياتين في مصل الدم بالاضافه الى قياس حامض اليوريك وبأستعمال العدد الخاصة.

سبعة عشر (56.7%) من المرضى كرروا التعرض للهالوثين بأجراء عمليات جراحيه مسبقه ، و 13 (43.3%) أجروا عملية جراحية واحده.

لا تغير معتد يلاحظ بالنسبه لجنس المرضى لهذه المعالم . نستنتج بذلك ان القيم المختبريه بعد العملية الجراحيه مباشرة وعلى مدى ثلاثة ايام لم تظهر أي أتجاه نحو اختلال كبير في وظائف الكليه المصابه.

Introduction

Halothane is (Fluothane) inhalational aneasthetic agent, it is a hydrocarbon molecules (trifloro-bromo-chloroethane) have a formula C2F3HBrCl. Introduced in 1956, were the first of the modern, and halogenated inhalational anesthetics used in clinical practice. It is a potent agent that is used for maintenance of anesthesia. [1] Patients anesthetized with halothane usually produce a small volume of concentrated urine. This is consequence of halothane-induced reduction of renal blood flow and glomerular filtration rate. [1] Halothane, at the present time is widely used as inhalational anesthetic in Basrah, and at times is the only one. This has made a good opportunity to investigate its effects on abnormal renal function tests in our local patients who are exposed to it. In addition, drugs like analgesics and antibiotics are, also, heavily used particularly in the postoperative period. Several of these drugs can compromise renal functions. All these factors form the basis for conducting the present study.

Metabolism (biotransformation, biodegradation) of halothane in humans is at least 20% [2] and possibly as great as 46% of administrated drug, depending on the method of measurement used. This compares with 2-8% of enflurane[3], less than 1% of isoflurane and 0.02% of desflurane [4].

The major metabolite of halothane is trifluoroacetic acid, which is formed by removal of bromine and chlorine ions [5]. Trifluoroacetic acid, bromine, and chlorine ions all can be detected in the urine. Trifluoroacetylchloride, an intermediate in oxidative metabolism of halothane, can triacetylate several proteins in liver–kidney microsomes [6]. Halothane –induced changed in renal function are fully reversible and are not associated with long-term nephrotoxicity [1]. The kidneys are critical in elimination of waste products, and alteration in renal function is one of the more common causes of drug toxicity due to inadequate excretion of medications or their metabolites [7]. Biochemical assessment of renal dysfunction during and after anesthesia usually includes measurement of blood urea nitrogen (BUN) and serum creatnine as well as serum uric acid. Urea is the waste product of amino acid metabolism, produced from ammonia in the hepatic urea cycle by convention, urea results are usually expressed as blood urea nitrogen (BUN), non-protein nitrogen was used as a test of renal function and most non-protein nitrogen is in urea. [8]Creatinine is a waste product of muscle creatine. The rate of creatinine production is related to muscle mass, activity, and ingestion of creatine in meat as well as total protein intake; these variables also affect plasma creatinine levels. [9]Uric acid is the final breakdown product of nucleic acid and purine catabolism in humans. [10] The aim of present study was to estimate the effects of halothane anesthesia on renal function tests in patients with abnormal renal diseases.

Patients and Method

In Basrah General Hospital a total of (30) patients with a mean age (39.1± 17) years, 46.7% (14) of them males and

(16) 53.3% were females. These patients with abnormal renal function [an elevated of blood urea, serum creatinine and serum uric acid] underwent surgical operation under general anesthesia using of halothane 1-3 % v/v in 100% oxygen for different times of exposure (ranged 10-180 minutes). Anesthesia was induced by 6 mg/kg body mass thiopentone 2.5 % intravenously (i.v) and endotracheal intubation was facilitated with (i.v) injection of 1 mg/kg of succinylcholine; then muscle relaxation maintained by (i.v) pancuronium 0.1 mg/kg body mass. At the end of surgery residual muscle relaxation was reversed using neostigmine 2.5 - 5 mg (i.v) mixed with atropine 1.5 mg in same syringe. Monitoring during anesthesia for vital signs includes indirect arterial blood pressure, pulse rate, oxygen saturation by pulse oximetry and electrocardiographic monitoring.

These patients had different types of surgical operations and they were receiving different regimens of antibiotic and analgesic drugs. A follow-up form was filled for each patient. This includes name, age, gender, type of operation, occupation, as well as medical history for any previous illness and type of treatment, and for any previous surgical operation.

After an average preoperative fasting for 6-12 hours, venous blood samples (5 ml) were taken by a sterile disposable syringe then collected in plain plastic tubes in the following time intervals; immediately before (control) and after operation and then followed-up at the 1st and 3rd postoperative days.

The serum was separated immediately after withdrawal and stored in refrigerator at -4°C. until analyzed, and was investigated for different parameters of serum levels for kidney function tests by using diagnostic kits which include: {urea kit BioMeieux No. 61912 normal range(16-45mg|dl) [11],creatinine kit BioMeieux No. 61 162 normal range(0.7-1.4mg|dl)[12], and (uric acid kit Ccromatest No. 1161010 normal range (3.5-7.2mg|dl)[13]}. These patients had different types of surgical operations and they were receiving different regimens of antibiotic and analgesic drugs.

Due to unavoidable circumstances, not all the parameters were estimated that is because of some patients were discharged one or 2 days after operation.

Data were analyzed statistically using SPSS computer package, version 11. ANOVA and paired t-test were used to test the significance of results. $P < 0.05$ was taken to be the lower limit of significance.

Results

Characteristics of the patients in this study are shown in (Table 1).

(Table 2) show frequency of halothane exposures in previous surgeries, 17 (56.7%) had repeated exposure to halothane by underwent previous surgeries and 43.3% (13) are newly exposure to halothane in the study period.

There was no statistically significant for blood urea levels on post operative period when compared preoperatively, its changes from 59.3 to 52.9 and 48.5 mg/dl at 1st and 3rd days respectively (Table 3).

There was no significant change for sCreatinine levels on post operative period when compared to preoperatively, its changes from 2.1 to 1.6 and 1.4 mg/dl at 1st and 3rd days respectively, but its statistically significant decreases ($P<0.05$) only at immediately

postoperatively, its change from 2.1 to 1.6 mg/dl (Table 3).

Serum uric acid levels changes from 9.7 to 6.5 and 5.9 mg/dl at 1st and 3rd days respectively (Table 3).

There was not statistically significant observed for males and females patients over 3 days follow up period, also no statistically difference between them was seen (Table 4).

Table 1 Patients characteristics

Patients characteristics		**No.**	**%**
Age Total age range (10-70)years	Mean age (39.1± 17)years	30	100
	10-25 years	6	20
	26-45 years	14	46.7
	46-70years	10	33.3
Gender	Males mean age (41.2±17.8) years	14	46.7
	Females mean age(38.6±17) years	16	53.3
Type of surgery	Kidney, bladder & prostate (laparotomy)	12	40
	Transurethral resection of prostate (TURP)	8	26.6
	Upper & lower limbs surgeries	6	20
	Hepatic hydatid cysts removal & laparoscopic cholecystectomy	4	5.4
Duration of halothane exposure range(10-180) (minutes)	<45	8	26.7
	45-90	9	30
	>90	13	43.3
Smoking habits	Smoker	7	23.3
	Non smoker	23	76.7

Table 2 Frequency of halothane exposures in previous surgeries

Frequency of halothane exposures	Number of patients	%
0	13	43.3
1	8	26.7
2	5	16.7
3	4	13.3
Total	30	100

Table 3 Renal function tests for patients with renal diseases mean± SD(n)

Renal function tests	**Immediate Pre-operative Period**	**Post–operative Period**		
		Immediately	**1st day**	**3rd days**
Serum urea (mg/dl)	59.3 ±23.1 n=30	43.4± 18.8 n=30	52.9 ±13.2 n=21	48.5 ±18.5 n=12
Serum creatinine (mg/dl)	2.1±0.5 n=30	1.6± 0.8 * n=30	1.6±0.67 n=21	1.4±0.7 n=12
Serum uric acid (mg/dl)	9.7±3.9 n=10	7.9±2.0 n=10	6.5 ±1.4 n=5	5.9±1.3 n=5

* P <0.05

Serum urea normal range (16-45mg|dl); serum creatinine normal range (0.7-1.4mg|dl); serum uric acid normal range (3.5-7.2mg|dl); SD=standard deviation; (n) =number of patients.

Table 4 Renal function tests for males (M) and females (F) with renal diseases mean ± SD (n)

Renal function tests Males& females		Immediate Pre-operative period	Post–operative periods		
			Immediately	1st day	3rd days
Serum Urea (mg/dl)	M	52.3±19.1(14)	37.4±17.3(14)	51.6±7.3(6)	32.4±1.1(4)
	F	65.8±25.2(16)	48.9.±19(16)	53.4.±15.3(15)	54.9±18(8)
Serum Creatinine (mg/dl)	M	2.33±0.4(14)	1.54±0.4(14)	1.7±0.3(6)	1.07±0.3(4)
	F	2.1±0.5(16)	1.64±0.7(16)	1.57±0.7(15)	1.69±0.9(8)
Serum Uric acid (mg/dl)	M	9.0±4.1(9)	7.2±2.1(9)	6.6±1.8(4)	6.2±1.8(4)
	F	5.4(1)	7.6(1)	8.18(1)	8.72 (1)

Serum urea normal range (16-45mg|dl); serum creatinine normal range (0.7-1.4 mg|dl); serum uric acid normal range (3.5-7.2 mg|dl); SD=standard deviation; (n) = number of patients.

Discussion

Isoflurane, reduces renal blood flow and glomerular filtration rate, resulting in a small volume of concentrated urine. Changes in renal function observed during isoflurane anesthesia are rapidly reversed, with no long-term renal toxicities [14]. Egeret et al [15] controversy has surrounded the potential nephrotoxicity of compound A, the degradation produced by interaction of sevoflurane with CO_2 absorbent soda lime. Biochemical evidence of transient renal injury has been reported in human volunteers. Large clinical studies have shown no evidence of renal increased serum creatinine, blood urea nitrogen, or any other evidence of renal impairment following sevoflurane administration [16]. , the current recommendation of FAD is that sevoflurane be administered with fresh gas flows of at least 2 L/min to minimize accumulation of compound A [1].

Like other inhalational anesthetics, enflurane reduces renal blood flow, glomerular filtration rate, and urinary output. These effects are rapidly reversed upon drug discontinuation. Enflurane metabolism produces significant plasma levels of fluoride ions (20 to 40 µmol) and can produce transient urinary-concentrating defects following prolonged administration [17]. There is scant evidence of long-term nephrotoxicity following enflurane use, and it is safe to use in patients with renal impairment, provided that depth of

enflurane anesthesia and the duration of administration are not excessive [18]. Desflurane has no reported nephrotoxicity. This consistent with is minimal metabolic degradation [1].

The selection of a safe and effective drug regimen for patients with renal impairment can be difficult [19]. Data obtained from studies in people with normal renal function cannot be used to design drug therapy for patients with renal failure. Many drugs and their metabolites undergo renal excretion and therefore accumulate in renal failure. However, relatively little is known about the effect of renal impairment on drug metabolism by the liver [19].

Non-steroidal anti-inflammatory drugs (NSAIDs) are useful for the treatment of postoperative pain, but there is continuing concern about adverse effects on renal function[20], however, the renal effects of the non-steroidal anti-inflammatory drug had been studied in rats before and after surgery and 3 days' drug administration.[20] It was found that only ketorolac when given with the antibiotic gentamicin produced marked changes in kidney function and structure.[21] In addition, ketorolac was shown to be as safe as ketoprofen and diclofenac for treatment of pain after major surgery.[21]

The kidneys are involved in many critical body functions. They regulate fluid, electrolyte, and acid-base status by filtration of blood, followed by selective reabsorption from or secretion into the tubular fluid [7].

With progressive renal insufficiency there is retention in the blood urea, creatinine, and uric acid [22]. Normally the ratio of serum urea to serum creatinine is between 10:1 and 20:1. In the usual case of renal failure, a similar ratio is seen. Ratio higher than 20:1 occur in disease states of extra renal origin, such as pre renal azotemia, gastrointestinal bleeding, or excessive protein intake with marginally adequate renal function. Uric acid concentration in the blood rises in advanced chronic renal failure, but this rarely results in classical gout [22].

Urea in the blood is reported as the (BUN). Urea production and the BUN are increased when more amino acids are metabolized in the liver. [23] Plasma urea can rise whenever there is increase formation or decreased excretion of urea, or where there is dehydration. Increase formation occurs when the diet is high in protein, since amino acids formed from protein in excess of the body's requirements or because of its ability to metabolize them immediately to urea by the urea cycle. Endogenous protein breakdown is increased in catabolic states (e.g. in fever , after trauma) and the same cause is responsible in part for the uraemia that is often seen following gastrointestinal haemorrhage, as the blood protein are then digested and absorbed (24). The BUN is reduced in the presence of a low-protein intake and severe liver disease. Urea production exceeds renal urea excretion in normal persons; the remaining urea is degraded to ammonium ions by intestinal bacteria. Urea is readily filtered, but approximately 40% to 50% of the filtered urea is normally reabsorbed by the proximal tubules. Because many factors influence the BUN level, BUN is less specific indicator of renal function and should not be relied on for that purpose [25].

Urea is filtered by glomeruli and reabsorption occurs in the collecting ducts along with water under the influence of ADH [26]. In states of active water reabsorption, urea clearance

will be considerably less than GFR, while in states of water diuresis urea clearance will be closer to GFR. However, plasma urea may be altered for many physiological and pathological conditions other than renal disease [7].

Serum creatinine levels and urinary creatinine excretion are a function of muscle mass in normal persons and show little response to dietary changes [27]. Creatinine is derived from nonenzymatic dehydration of creatine in skeletal muscle. The amount of creatine per unit of muscle mass is constant, and thus the rate of spontaneous breakdown of creatine is also constant, as a results, the plasma creatinine concentration is very stable, varying less than 10% per day in serial observations in normal subjects. Because the serum creatinine concentration is direct reflection of muscle mass, the serum level is higher in males than females. Creatnine is freely filtered at the glomerulus and is not reabsorbed by the tubules [27].

In patients with known renal disease, plasma urea parallels plasma creatinine. However, because of the much closer relationship between plasma creatinine and GFR than between plasma urea and GFR, plasma creatinine is more suitable both for detecting, and for monitoring the progress of renal disease.

In patients with an increase in plasma urea that is relatively greater than the increase in plasma creatinine, the presence of one of the pre-renal causes of uraemia may be suspected. It can, therefore, be of value to have both measurements. Where only one or other investigation is offered, plasma creatinine is to be preferred [28].

Creatinine production is increased in sepsis, trauma, and after major surgery, but falls with increasing age, with muscle atrophy of any cause and in liver disease [25]. Drugs that compete with creatinine for secretory pathways can increase plasma creatinine. The most common drugs that block creatinine secretion include: cimetidine, trimethoprim and salicylates; each can increase plasma creatinine up to 20% to 30% from baseline levels. [27] While many factors can affect creatinine reference ranges, there is relatively little day-to-day variation of creatinine in a healthy individual, with average variation of about 5%. Therefore, small changes in creatinine from a person's baseline serve as sensitive markers for a change in renal function if other causes of altered creatinine can be eliminated [28].

Uric acid is derived from the oxidation of purine bases. Plasma levels of uric acid are quite variable and completely filterable, and both proximal tubular reabsorption and distal tubular secretion occur, with advanced chronic renal failure there is progressive increase in the plasma uric acid level [22]. Hyperuricemia is defined as serum urate concentration greater than 7 mg/dl and may result from a number of disorders and conditions associated with increased urate production and/or decreasesd renal excretion. Increased production of uric acid is seen in lymphomas and leukemias, ingestion of certain drugs (ethanol, cytotoxic drugs) excessive consumption of purine-rich foods (meats, viscera, vegetables). Decreased excretion is found in patients with essential hypertension, chronic renal failure, ketoacidosis, lactic acidosis, and use of diuretics (thiazides, furosemide). Several studies have found hyperuricemia to be independently associated with increased mortality in patients with cardiovascular and renal diseases [29]. In some individuals,

hyperuricemia may precipitate development of acute renal failure [29].

In this study, serum creatinine and BUN are slightly decreased postoperatively; this is similar to a study done by groudeine et al [30].

There were no changes in the abnormal laboratory values after general anesthesia for patients with renal disease. This is an agreement with the study of zaleski et al. [31] However, halothane has a low cost and therefore still is widely used in developing countries [1].

No marked effect of the drugs used during and after surgery on renal function was found in this study.

We conclude that, the laboratory values at immediately after surgical operations and for 3 days later, there was no trend for a major derangement for patients with renal disease. This is also agreements with the previous study undergoing for patients with normal renal function test that have been exposure to halothane anesthesia. [32]

Conclusion

Halothane anesthesia has no clinically significant effect on renal functions in patients with abnormal renal diseases.

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