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Comparison between low flow sevoflurane anesthesia and total intravenous anesthesia during intermediate-duration surgery: effects on renal and hepatic toxicity

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Abstract

Background: Renal and hepatic dysfunction or injury might be involved by ether based anesthetic and intravenous anesthetic drug or surgical stress. The purpose of this study is to compare the effect of moderate duration low-flow sevoflurane versus total intravenous anesthesia on renal and hepatic functions.

Patients and Methods: Eighty (80) patients between the ages of 25-70 scheduled for elective lumbar disc herniotomy, with an expected operation time of 120-240 min, were enrolled in the study. Anesthesia was induced using remifentanil, propofol and atracurium. Patients were randomly divided into two groups. After intubation, Group S (n=40) received sevoflurane and Group T (n=40) received total intravenous anesthesia with propofol in oxygen and air with a fresh gas flow of 5 L min^{-1}. Ten minutes after induction the fresh gas flow was decreased to 1L min^{-1} in both groups. Serum BUN, creatinine, ALT, AST, LDH and 24 hours excretion of glucose, protein, and creatinine in urine were measured preoperatively and the first three postoperative days.

Results: Serum BUN at 48 hours, creatinine at 24, 48. hours, and urine glucose at 24, and 48 hours were significantly higher from the preoperative values in Group S ($p<0.05$). However, serum BUN and creatinin, urine glucose were within the normal range. There were no significant differences in the renal and hepatic function tests between the groups.

Conclusions: These results show that the renal and hepatic effect of moderate duration low-flow sevoflurane and total intravenous anesthesia is similar. Hippokratia 2011; 15 (1): 69-74

Key words: anesthesia, general, sevoflurane, low, flow anesthesia, analgesics, opioid, remifentanil, propofol, kidney

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Over the past 10 years, low-flow anaesthesia has been widely used in adult anesthesia practice. Low-flow anesthesia significantly reduces wastage of expensive volatile anesthetic agents and prevents air pollution[1].

Sevoflurane is partly degraded by carbon dioxide absorbents during low-flow to fluoromethyl-2,2-difluoro-1-(trifluoromethyl) ether (Compound A)[2]. Compound A is a dose-dependent nephrotoxin in rats[3,4]. Most of the authors investigated standard clinical measurements of renal function (Blood urea nitrogen (BUN), serum creatinine), but found no clinically significant effect of low-flow sevoflurane on renal function in surgical patients[5,6].

Sevoflurane and desflurane have a lower solubility in blood and tissues than all previous volatile anesthetics[7]. However, damage to renal and hepatocellular tissues occurs after the administration of general anesthesia with all modern inhaled anesthetics[8]. Renal and hepatic dysfunction/injury might be involved by ether based anesthetic and intravenous anesthetic drug or surgical stress. Objective measurements of the degree of liver and renal dysfunction are difficult. Raising renal and hepatocellular enzyme markers and clinical measurments can be observe because of this injury[9].

Total intravenous anesthesia (TIVA) was provided good haemodynamic stability. Hemodynamic stability is a determining factor of the hepatic and renal response to low-flow anesthesia[10].

In this study we aim to compare the effects of low-flow sevoflurane anesthesia versus total intravenous anesthesia on renal and hepatic functions during a surgery of moderate duration.

Patients and Methods

This study was approved by the Committee for Ethics in Human Research, and informed consent was obtained from each patient individually. Eighty patients undergoing elective lumbar disc herniotomy with an expected operative time of 120-240 min were enrolled in this prospective, randomized, single-blinded study. Any history of known liver disease or preexisting liver dysfunction [alanine aminotransferase (ALT) or aspartate aminotransferase(AST) >40 UL^{-1}], renal insufficiency (creatinine >1,5 mg dl^{-1}), abuse of alcohol or drugs, diabetes, unstable angina pectoris and a history of myocardial infarc-

tion within the last 6 months were defined as exclusion criteria.

Patients were premedicated with midazolam (0.05 mg kg^{-1}; im) 30 minutes before the operation and were randomized to receive either sevoflurane or total intravenous anesthesia. Patients were monitored with pulse-oximetry, electrocardiogram, cutaneous temperature (T), noninvasive blood pressure (NIBP), and end-tidal carbon dioxide ($ETCO_2$). Anesthesia was induced by using propofol (2 mg kg^{-1}) (Propofol 1% Fresenius; Fresenius Kabi**,** Australia GmbH), remifentanil (1 µg kg^{-1}) (Ultiva® GlaxoSmithKline, Genval, Belgium) and atracurium (0.5 mg kg^{-1}) (Tracrium®, GSK, Genval, Belgium). After induction anesthesia was maintained in Group S (n=40) using sevoflurane (Sevorane®, Abbott Lab, North Chicago, ABD) in concentration 0,8-2.5 %, remifentanil (0.20 µg kg^{-1} min^{-1}) and atracurium (0,5mg kg^{-1}) infusion were given in oxygen (50 %) and air at a total fresh gas flow of 5 L min^{-1} that was decreased to 1 L min^{-1} after 10 min. Maintenance in Group T (n=40) was achieved by using 100 to 168 µg kg^{-1} min^{-1} propofol and 0.20 µg kg^{-1} min^{-1} remifentanil, atracurium (0,5mg kg^{-1}) infusion total gas flow of 5 L min^{-1} that was decreased to 1 L min^{-1} after 10 min.Ventilation was controlled with a tidal volume of 8 ml kg^{-1}, with the ventilatory (Dräger® Julian, Lübeck, Germany) rate adjusted to maintain a $PaCO_2$ of 30 to 40 mmHg. Fresh barium hydroxide was used to fill the carbon dioxide-absorbent canister before each case. A threshold of hypotension was defined as a mean arterial pressure of <70 mmHg for more than 10 min in both groups. Hypotensive episodes were treated by increasing the rate of fluid administration (lactated Ringer's solution) and/or by reducing the anesthetic drug concentration. Bradycardia was defined as <45-50 beats min^{-1} in both groups. Bradicardia episodes were treated with atropine.

Ten minutes before the end of the surgery, the anaesthetic gases were stopped and fresh gas flow was increased from 1L to 5 L min^{-1}. Extubation was performed after decurarization with atropine and neostigmine administration. Postoperative antibiotics were restricted to 2 g $day^{-1}$of cefazolin up to 3 days after anesthesia. Nonsteroidal anti-inflammatory drugs were not allowed through the intraoperative and postoperative period. Venous blood urea nitrogen (BUN), creatinine, ALT, AST, lactate dehydrogenase (LDH) and 24 hours of glucose, protein, creatinine in urine were measured and recorded preoperatively and during each of the first three postoperative days. All samples were analyzed by the laboratory personnel, who were blinded to the anesthetic randomization. Normal values are as follows: BUN (10-50 $mgdl^{-1}$), creatinine (0-1.5 mg dl^{-1}), AST (0-37 IUL^{-1}), ALT(0-41 IUL^{-1}), LDH (240-480 IUL^{-1}), urinary glucose (76-115 mg dL^{-1}), protein (0-150 $mg.day^{-1}$) and creatinine (800-1800 mg day^{-1}) (Beckman Coulter CX9, Florida, USA). Vital signs and clinical status were assessed daily postoperative.

Isotonic solution (9% NaCl) 5-6 $ml.kg^{-1}.h^{-1}$ was administered during anesthesia and at a rate of 2 $ml.kg^{-1}.h^{-1}$ for 16 h after cessation of anesthesia.

Statistical analysis. The numeric results were expressed as mean±sd, and categorical results were expressed as a number. Normality distribution of the variables was tested using one sample Kolmogorov Smirnov test. Differences between groups were assessed using the Student's t test for normal, Mann Whitney U test for non-normal distributed data. The chi-square test was used to compare the differences of categorical variables between the groups. Analysis of Covariance (ANCOVA) test was used to analyze changes from Preanesthesia to postanesthesia at 24, 48, and 72 hours. Statistica 7.0 (StatSoft Inc. Tulsa, OK, USA) statistical software was used for statistical analysis. A p value <0.05 was considered statistically significant.

Results

Eighty consenting patients were included in this study. Patients anesthetized with sevoflurane and total intravenous anesthesia were similar with respect to age, sex, Body Mass Index (BMI), anesthesia time, ASA physical status and total amount of remifentanyl (Table 1). There were no differences in the preoperative laboratory values from the urine and blood samples between the groups (p>0.05) (Tables 2,3). No patients in any of the two groups had preoperative or postoperative laboratory values in excess of the upper limit of the normal range.

Serum AST, ALT, LDH were used to determine the effect of anesthesia on the liver. There was no significant difference between the two groups (p>0.05) (Table 2).

The renal function in the two groups was also compared by serum BUN, creatinine and urinary excretion of glucose, protein, and creatinine. Serum BUN was significantly increased at 48 hrs compared to the preoperative values in group S, whereas there was no significant difference between the two groups (p<0.05) (Table 2). Se-

Table 1: Patient characteristics, anesthesia time and total amount of remifentanyl (mean values±SD).

	Group S (n = 40)	**Group T (n = 40)**
Age (yr)	36.5±7.6	35.1±6.2
Sex (female/male)	19/21	18/22
BMI	26.6±2.3	26.4±1.4
Anesthesia time (min)	123.5±32.0	132.0±19.2
ASA (I / II)	21/19	18/22
Peroperative Remifentanil (µg)	2130±43	1999±32

BMI: Body Mass Index
ASA; American Society of Anesthesiology

rum creatinine was significantly different at 24 and 48 hrs compared to the preoperative values in group S, whereas again there was no significant difference between the two groups. ($p<0.05$) (Table 2).

Urine glucose at the 24, 48.hours were significantly increased from preoperative values in the group S ($p<0.05$) (Table 3). However there was no significant difference between the groups. Urine creatinine was no significantly different at 24., 48. and 72. hours between the groups (Table 3).

There were no significant hypotension or bradycardia episodes intraoperatively in neither group. The amount of peroperative remifentanil used was similar in both groups. Measurements of blood pressure and heart rate did not differ among the two groups. Postoperative use of analgesic drugs was also similar in both groups. ἐntraoperatively, there were no differences in total crystalloid and colloid consumption, and estimated blood loss.

Discussion

The results of this investigation demonstrate that the effects of low-flow sevoflurane anesthesia and total intravenous anesthesia on renal and hepatic functions during moderate duration surgery were not significantly different. Postoperative renal and hepatic functions in both groups was similar, as assessed with serum BUN, creatinine, AST, ALT, LDH and urine excretion of glucose, protein and creatinine.

Many anesthesia practices and surgical procedures, such as antibiotics, surgical stress, preexisting renal disease, intraoperative blood pressure, site of surgery, and anesthetics have been implicated in the cause of renal and hepatic dysfunction /injury, but none have been controlled for in prospective studies[11]. Our study demonstrated that postoprative serum BUN, creatinine and urine glucose values were increased when compared to the preoperative values in group S. There was no differ-

Table 2: Serum BUN, creatinine, AST, ALT, LDH were preoperative and postoperative values in the sevoflurane and TIVA group (mean values±SD).

		Group S (n = 40)	Group T (n = 40)	P value (Grup S vs. Grup T)	P value (Δ (change) Preanesthesia; Grup S vs. Grup T)
BUN(mgdL^{-1})	**Preanesthesia**	33.9±6.1	32.8±6.6	0.463	
	Postanesthesia 24h	33.8±6.2	31.5±9.1	0.183	0.235
	Postanesthesia 48h	35.0±6.7	32.2±8.5	0.060	**0.014**
	Postanesthesia 72h	35.1±5.8	32.2±8.3	0.070	0.080
Creatinine(mgdL^{-1})	**Preanesthesia**	0.8±0.2	0.9±0.7	0.312	
	Postanesthesia 24h	0.9±0.2	0.9±0.2	0.328	**0.043**
	Postanesthesia 48h	0.9±0.2	0.8±0.2	0.207	**0.012**
	Postanesthesia 72h	0.9±0.2	0.9±0.2	0.736	0.196
AST(IUL^{-1})	**Preanesthesia**	25.9±7.4	24.7±7.4	0.453	
	Postanesthesia 24h	25.9±6.7	25.4±7.7	0.769	0.822
	Postanesthesia 48h	28.1±7.4	26.2±7.0	0.231	0.353
	Postanesthesia 72h	28.8±9.2	26.5±7.8	0.235	0.361
ALT(IUL^{-1})	**Preanesthesia**	26.3±9.3	26.1±8.8	0.921	
	Postanesthesia 24h	24.6±9.5	21.7±11.6	0.224	0.099
	Postanesthesia 48h	24.9±8.3	22.6±9.7	0.243	0.112
	Postanesthesia 72h	25.8±8.8	24.2±10.9	0.478	0.302
LDH(IUL^{-1})	**Preanesthesia**	287.0±36.2	284.8±39.6	0.791	
	Postanesthesia 24h	292.5±39.2	294.0±45.6	0.877	0.289
	Postanesthesia 48h	304.4±42.6	296.9±43.5	0.434	0.262
	Postanesthesia 72h	310.1±34.8	297.6±37.5	0.124	0.056

BUN; blood urea nitrogen, ALT; alanine aminotransferase, AST; aspartate aminotransferase, LDH; lactate dehydrogenase.

ence among the two groups. These mild abnormalities in renal function were thought to be due to the surgical stress.

The previous study used fentanyl as an analgesic drug for low-flow anesthesia[11]. However we have used remifentanil infusion intravenous with low-flow sevoflurane and propofol intravenous anesthesia. Muellejans et al[12] reported that remifentanil was well tolerated and provided good haemodynamic stability – similar to that observed in patients receiving fentanyl, which is the current 'gold standard' for the provision of haemodynamic stability in the Intensive Care Unit setting. One of the most significant advantages of remifentanil is its organ independent mode of metabolism. This makes it particularly valuable for use in patients with organ impairment[13]. Intraoperative haemodynamic stability is very important for the effect of renal and hepatic responses to low-flow anesthesia.

Sevoflurane degradation by carbon- dioxside absorbents during low-flow anesthesia forms the haloalkene Compound A, which causes nephrotoxicity in rats. Many studies have shown no effects of Compound A formation on postoperative renal function after moderate duration (3-4 h) in low-flow sevoflurane[6]. The time spent at low-flow anesthesia has the effect of increasing compound A concentrations for the first 2 hours, after which the level plateaus. Frink et al[14] detected a reduction in the production of compound A after 2 hours and a fall in compound A levels after 4 hours[15]. In our study the mean anesthesia time is between 124-132 min.

Eger et al[16] reported that when volunteers were administered sevoflurane for 2- 4 hours, renal injury markers did not change after 2 hours of sevoflurane anesthesia; however, slight albuminuria and increased urinary α glutathione-S-transferase (GST) were found after 4 hours of sevoflurane anesthesia. Therefore, they postulated that the threshold for renal injury in humans is between 80 and 168 ppm-h of Compound A. In contrast, another study observed that with the same setting, neither 4 hours nor 8 hours of sevoflurane anesthesia caused any significant effects on renal function[17,18]. We could not measured the circuit concentrations of Compound A, but renal effect of anesthesia were measured by serum BUN, creatinine and urinary excretion of glucose, protein, and creatinine. Similar to this study, neither 120, nor 240 min, of low-flow sevoflurane anesthesia administration caused any significant effects on renal function.

Serum creatinine is not a very sensitive marker of kidney function. It may reflect a major acute change in kidney function that ought to be investigated with more sensitive methods such as glomerular filtration rate (GFR) with 51-Cr-EDTA. Renal function were assessment by serum BUN, creatinine and urinary excretion of glucose, protein, and creatinine in our study. Because we could not measured GFR with 51-Cr-EDTA[19].

Kharasch et al[6] reported no significant differences between the renal effects of sevoflurane and isoflurane

Table 3: Urine glucose, protein and urine creatinine were preoperative and postoperative values in the sevoflurane and TIVA group(mean values±SD).

		Group S (n = 40)	Group T (n = 40)	P value (Grup S vs. Grup T)	P value (Δ (change) Preanesthesia; Grup S vs. Grup T)
Urinary Glucose(mg.dL^{-1})	**Preanesthesia**	87.3±6.5	85.6±5.3	0.195	
	Postanesthesia 24h	88.0±7.2	84.9±7.5	0.065	**0.041**
	Postanesthesia 48h	87.3±9.3	83.0±8.5	0.060	**0.023**
	Postanesthesia 72h	85.0±10.8	84.9±6.6	0.951	0.853
Urinary Protein (mg.day^{-1})	**Preanesthesia**	80.5±19.6	79.9±17.2		
	Postanesthesia 24h	122.5±84.3	105.3±35.3	0.623	0.226
	Postanesthesia 48h	143.8±106.0	126.1±117.0	0.152	0.494
	Postanesthesia 72h	149.9±136.1	130.6±134.3	0.066	0.330
Urinary Creatinine (mg.day^{-1})	**Preanesthesia**	1005.3±165.8	1004.3±162.8	0.836	
	Postanesthesia 24h	1480.6±465.0	1329.9±400.9	0.164	0.109
	Postanesthesia 48h	1614.2±1017.7	1599.4±1020.8	0.870	0.947
	Postanesthesia 72h	1209.3±500.4	1118.8±390.6	0.233	0.367

in surgical patients undergoing long-duration low-flow anesthesia for up to 17 hours, by using serum creatinine, BUN, creatinine clearance, or urinary protein or glucose excretion. There was no correlation between Compound A exposure and any of the renal function variables. No evidence for low-flow sevoflurane nephrotoxicity was observed, even at large Compound A exposure. Proteinuria and glucosuria were common and nonspecific postoperative findings. Our study demonstrated that postoperative serum creatinine, BUN and urine glucose values were significantly higher than preoperative values in the sevoflurane group. But these laboratory findings were in the normal range.

The authors reported that the serum creatinine level was unchanged from preoperative values in propofol and sevoflurane anesthesia. No effects attributable to propofol in patients with and without renal failure have been documented using serum creatinine and BUN[20-23]. In this study, serum BUN, creatinine and urine glucose were unchanged from preoperative values in the total intravenous anesthesia with propofol group.

Sevoflurane anesthesia has been administered to more than one million patients in Japan, with four reports of associated hepatotoxicity[24]. Obata et al[4] reported that prolonged low-flow sevoflurane anesthesia has the same effect on renal and hepatic functions as high –flow sevoflurane and low- flow isoflurane anesthesia. We reported that serum AST, ALT and LDH were not significantly different between sevoflurane and TέVA anesthesia.

Hexafluoroisopropanol (HFIP) and inorganic fluoride are the products of sevoflurane metabolism. The HFIP is rapidly excreted by the kidneys. Even though we did not detect any metabolites of sevoflurane degradation, it seems unlikely that sevoflurane per se or its metabolites causes hepatocellular impairment[9,25].

Several studies observed that the effects of inhaled anesthetics on human hepatic function produced similar results with aminotransferase activity[8]. Increased serum levels of aminotransferase activity were regarded as the "gold standard" for anesthetic-related hepatic toxicity. These enzymes lacks specificity, because a variety of organs other than the liver contain aminotransferases[9].

Propofol (2,6-diisopropylphenol) is a rapid-onset, short-acting intravenous anaesthetic agent that is widely used for anaesthesia[26]. Previous investigations have shown that propofol interferes with the metabolism of co-administered drugs via animal and human liver phase-I metabolizing enzymes. There are several roads of evidence indicating that propofol induces subclinical and reversible disturbance in hepatocelular integrity by affecting the serum level of hepatic transferase (conjugation) enzymes in vivo after long-term infusion[27,28]. The exact effect of propofol on the functional activities of specific phase-II conjugation enzymes has not yet been investigated.

In conclusion, we assessed the effect of moderate duration low-flow sevoflurane versus total intravenous anesthesia on renal and hepatic functions using practical, easily obtainable laboratory tests. We conclude that hemodynamic stability provided with both anesthetic techniques whereas both anesthetic techniques did not offer any superiority.

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