BIOCHEMICAL EFFECTS OF LOW-FLOW ANESTHESIA WITH INHALATION AGENTS IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERY

BIOHEMIJSKI EFEKTI ANESTEZIJE NISKOG PROTOKA INHALACIJSKIM AGENSIMA KOD PACIJENATA PODVRGNUTIH LAPAROSKOPSKOJ HIRURGIJI

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Summary: This study was designed to investigate the effects of low-flow anesthesia with sevoflurane and desflurane on renal and hepatic functions in patients undergoing laparoscopic abdominal surgery. Twenty patients with ASA I or II (American Society of Anesthesiologists classification) physical scores were included in the study. There were no significant differences between sevoflurane and desflurane groups with respect to age, weight, body mass index, duration of the operation and the anesthesia. In both groups, renal function parameters such as urea, BUN, creatinine and calculated creatinine clearance did not show significant differences at 24 and 48 hours. Homocysteine levels, which showed renal metabolic function, did not change significantly at 24 and 48 hours when compared to baseline levels in both groups. Transaminases were not significantly different between the two groups from baseline to 24 and 48 hours. These differences between the preoperative and postoperative values of biochemical parameters were similar for both anesthetic groups (p>0.05). Low-flow anesthesia did not cause impairment in terms of renal and hepatic functions.

Keywords: biochemical parameters, homocysteine, free radicals, volatile anesthetics, low-flow anesthesia

Introduction

A wide range of intraabdominal surgical procedures are increasingly being performed laparoscopically (1). In laparoscopic surgery patients, fresh gas flow rates and the kind of anesthetic agents used are important from the point of view that they have different effects on the organ systems. Differences emerge from the blood/gas and tissue/blood solubility coefficients of these drugs (2). Therefore, low-flow anesthesia is mostly preferred because it has the advantages of less anesthetic consumption, decreased atmospheric pollution and reduced cost in laparoscopic surgery. Especially, new volatile agents such as sevoflurane or desflurane are being used (3). In previous clinical studies no adverse effects of sevoflurane anesthesia were shown at various rates of fresh gas flow in normal renal function (4).

In vivo and in vitro degradation of sevoflurane produces inorganic fluoride and vinyl ether (Compound A), which has the...
potential to harm renal and hepatic function. In rats, it was shown that both degradation products from sevoflurane given with fresh gas flows of ≤ 2 L/min have not demonstrated nephrotoxicity. But, such studies usually assess renal function by changes in serum creatinine or blood urea nitrogen (BUN) (2). In a previous study, it was indicated that the fluoride resulting from sevoflurane anesthesia at a higher fresh gas inflow rate (normal range: 2–6 liter/min) did not produce renal injury in humans (7). Kharasch et al. (8) compared the effects of long duration (9.2±3.6 MAC hours) low-flow sevoflurane anesthesia (LFSA) and isoflurane anesthesia on renal and hepatic functions. They reported that CpA of volatile agents had no significant effect on renal function unless it was higher than 100 ppm/h in LFSA. However, it was indicated that prolonged administration of high concentrations of sevoflurane might lead to significant transient glomerular, proximal and distal tubular injury (9–11). Homocysteine, which is a specific and sensitive marker of renal metabolic function, is an amino acid that is a sulfur-containing metabolite of methionine. In the homocysteine metabolism, there are two major pathways – remethylation back to methionine using vitamin B₂ as a cofactor, and the second pathway is transsulfuration to cysteine using vitamin B₆ as a cofactor. Besides, desflurane causes carbon monoxide poisoning by producing carbon monoxide as enflurane and isoflurane do (8). Carbon monoxide can significantly elevate carboxyhemoglobin concentrations and it is not known if carboxyhemoglobin is degraded to difluorovinyl products, which are nephrotoxic (5, 12). Desflurane and sevoflurane were reported to have no adverse effects on hepatic metabolic function and most of the clinical studies have shown that low-flow anesthesia with desflurane and sevoflu-rane did not change renal and hepatic functions as well (13–15). Although it was demonstrated that desflurane and sevoflurane might affect renal and hepatic functions in open surgery, to our knowledge, this was not researched in laparoscopic surgery. This study was designed to investigate the effects of sevoflurane and desflurane with low-flow anesthesia (1 L/min) on renal and hepatic functions in patients undergoing laparoscopic abdominal surgery.

Materials and Methods

Subjects

Twenty patients with an ASA I-II (the American Society of Anesthesiologists classification) physical score undergoing laparoscopic abdominal surgery were included in this study. Informed consent was obtained from each patient. The study was conducted in accordance with the ethical standards of the Helsinki Declaration. The demographic characteristics of all subjects, matched for age, height, weight, body mass index (BMI), the duration of anesthesia and surgery, are shown in Table I. Patients who had any metabolic, endocrine, hepatic, or renal disease were excluded from the study.

Methods

Twenty patients were selected randomly to receive sevoflurane (n=10) and desflurane (n=10) by using randomization schemes at a fresh gas flow rate of 1 L/min. Fresh sodalyme® (Drager Healthcare Products, Inc., Germany) was placed into the canister in both groups immediately before the anesthesia. The patients were premedicated with 0.15 mg/kg intravenous midazolam and 10 μg/kg atropine 30 min before the induction of anesthesia. Anesthesia was induced with propofol (2–2.5 mg/kg), fentanyl (2–3 μg/kg) and rocuronium bromur (0.5 mg/kg) in 100% oxygen. After tracheal intubation, the fresh gas flow rate was set to 4.4 L/min in both groups. After 5 minutes the total fresh gas flow was reduced to 1.0 L/min. The ratio of oxygen to airflow rates was adjusted to maintain the oxygen concentration in the inspiratory limb at 50%. The anesthetic concentration was adjusted to maintain 1.5–2.0% for sevoflurane and 4–6% for desflurane with systolic blood pressure within ±20% of baseline. An intravenous bolus of 1–2 μg/kg fentanyl and 0.2 mg/kg rocuronium bromur were added in 30 min periods. Ventilation was controlled with a tidal volume of 10 mL/kg and the respiratory rate was adjusted to maintain an end-tidal carbon dioxide (EtCO₂) value between 35 and 45 mmHg. The anesthetic device used was Datex-Ohmeda ADU® Anesthesia System (Datex-Ohmeda, S/5, Helsinki, Finland). Postoperative antibiotics were restricted to 1 g/d of ceftriaxone up to 3 days after anesthesia.

Procedures

All patients were monitored by electrocardiography (ECG), for noninvasive blood pressure (BP), peripheral oxygen saturation (SpO₂) and end-tidal CO₂. During anesthesia, the end-tidal CO₂ concentration and inspired and end-tidal anesthetic concentrations were monitored by mass spectrometry (Datex-Ohmeda, ADU, S/5, Helsinki, Finland). The radial artery was cannulated to permit blood samples to be obtained for serum biochemical analysis before and after anesthesia. Blood samples were obtained before anesthesia and at 24 and 48 hours after the anesthesia for measurement of blood urea nitrogen (BUN), serum urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), direct bilirubin, total bilirubin and homocysteine levels. All serum urea, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate
dehydrogenase (LDH), gamma glutamyl transferase (GGT), direct bilirubin and total bilirubin analyses were performed by a central commercial laboratory that used an auto analyzer. Creatinine levels and AST, ALT activities were determined on a Hitachi-917 automated analyzer by using commercial kits supplied by Roche Diagnostics (Mannheim, Germany). Homocysteine level was determined by using a commercially available human ELISA kit (Med Systems Diagnostics GmbH, Vienna, Austria) (normal range for adults: 5–15 μmol/L). Creatinine clearance was interpreted by the Cockcroft-Gault formula (estimated creatinine clearance = [(140 – age in years) × weight in kilograms]/[72 × serum creatinine concentration in milligrams per deciliter); multiplied by 0.85 for women) (16).

Statistical analysis

Data are given as mean values ± standard deviation. Intergroup comparisons of the patient characteristics, anesthesia time, operation time, and serum biochemical concentrations were performed using Mann-Whitney U-test and Fisher’s protected least significant difference test. Inter and intragroup comparisons of laboratory data were performed using Friedman and Wilcoxon-rank test repeated measures analysis of variance. A p value < 0.05 was considered statistically significant.

Results

Demographic characteristics of the patients studied are listed in Table I. There were no significant differences between the two groups with respect to age, weight, BMI, duration of operation and anesthesia time. Renal function parameters such as urea, BUN and creatinine and calculated creatinine clearance did not show significant differences at 24 and 48 hours compared to baseline levels in both groups (Table II). Creatinine clearance (Cr) levels were found to be low at postoperative 24 (135.62±24.95/121.33±40.08) and 48 hours (122.35±40.39/104.80±27.29) compared to the baseline level (135.95±36.03/122.11±35.20) in sevoflurane and desflurane.

Table I

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane (n=10)</th>
<th>Desflurane (n=10)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>43.7±7.67</td>
<td>47.70±10.99</td>
<td>Ns</td>
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<tr>
<td>Height (cm)</td>
<td>163.8±4.10</td>
<td>163.7±5.86</td>
<td>Ns</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.7±7.30</td>
<td>76.70±9.48</td>
<td>Ns</td>
</tr>
<tr>
<td>BMI</td>
<td>27.2±3.05</td>
<td>28.95±3.89</td>
<td>Ns</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>7/3</td>
<td>5/5</td>
<td>Ns</td>
</tr>
<tr>
<td>Duration of anesthesia</td>
<td>105.5±18.02</td>
<td>100.50±18.62</td>
<td>Ns</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>93.0±17.02</td>
<td>90.50±17.86</td>
<td>Ns</td>
</tr>
</tbody>
</table>

*p<0.05 All values are expressed as mean± standard deviation, NS: not significant, BMI: body mass index.

Table II

<table>
<thead>
<tr>
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<th>Sevoflurane (n=10)</th>
<th>Desflurane (n=10)</th>
<th>P</th>
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<tbody>
<tr>
<td>BUN (mmol Urea/L)</td>
<td>11.75±3.35</td>
<td>12.07±3.71</td>
<td>ns</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>24.8±8.09</td>
<td>25.00±7.18</td>
<td>ns</td>
</tr>
<tr>
<td>Cr (μmol/L)</td>
<td>0.62±0.11</td>
<td>0.61±0.07</td>
<td>ns</td>
</tr>
</tbody>
</table>

*p>0.05 All values are expressed as mean± standard deviation, Ns: not significant, BUN: blood urea nitrogen, and Cr: creatinine (μmol/L).

Figure 1

Serum creatinine clearance (Cr) levels before and after low-flow anesthesia. The mean (dotted line), median, 25th–75th percentiles (box boundaries) and 10th–90th percentiles (whiskers) are shown. Outliers beyond 10%–90% are shown as individual data points. There were no significant differences between the anesthetic groups.
groups, respectively. These differences were not significant (Figure 1). Homocysteine levels which showed renal metabolic function did not change significantly at 24 (10.00±1.82/8.51±2.7) and 48 hours (9.44±0.96/8.51±2.7) compared to baseline (10.58±2.23/11.02±2.2) levels in both the sevoflurane and desflurane groups (Figure 2). Hepatic effects of low-flow anesthesia were tested by serum AST, ALT, GGT, LDH, direct bilirubin and total bilirubin concentrations. There were no significant differences between the two groups from baseline to 24 and 48 hours. There was no increase in the postoperative levels of hepatic function parameters in either of the anesthetic groups (Table III).

Differences between the preoperative and postoperative values (delta values) of biochemical parameters were similar for both anesthetic groups (p>0.05).

**Discussion**

To our knowledge, anesthesia techniques and surgery are important for changing the biochemical parameters. It was shown that surgery and anesthetic agents produced cellular oxidative toxic metabolites which damaged cellular function and tissue structure (17). It is preferred to cause minimal reactive oxygen species by using volatile anesthetic agents in low flow anesthesia (18). Especially in low flow anesthesia reactive oxygen species (ROS) are reduced due to the consumption of minimal sevoflurane and desflurane (19). Therefore, in low-flow anesthesia and laparoscopic surgery morbidity and mortality are reduced (1, 20).

Volatile anesthetics such as sevoflurane or desflurane produce oxidative toxic effects. Plasma ROS products are more decreased after the administration of sevoflurane than after desflurane, providing beneficial effects on the cellular metabolism now that biochemical oxidative products are decreased (2, 21). In our studies, we aimed to show the advantages of low-flow anesthesia with both sevoflurane and desflurane in laparoscopic surgery. Low-flow anesthesia (1–1.5 L/min) reduces the inhalation anesthetics consumption by nearly 40%–75%, compared to the circle system under high-flow anesthesia (2–6 liter/min). In addition, carbon dioxide (CO2) absorbents, which have been used in anesthesia rebreathing circuits, reduce the consumption of inhalation anesthetics (3, 22). The new anesthetics desflurane and sevoflurane, which are licensed for use in humans, offer theoretical and practical advantages over other volatile anesthetics. Sevoflurane has several properties which make it potentially useful as a maintenance anesthesia (23). The lower solubility of both agents provides improved control of delivery and faster rates of recovery compared with isoflurane or enflurane (24). Desflurane can cause airway irritation and sympathetic stimulation in humans. It causes a decrease in erythrocyte volume, which recovers after four days, and increases the

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**Table III** Comparison of hepatic functions between the two groups of patients.

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane (n=10)</th>
<th>Desflurane (n=10)</th>
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<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>24h postop</td>
<td>48h postop</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>23.00±7.7</td>
<td>24.50±9.2</td>
<td>24.50±9.2</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>20.00±7.1</td>
<td>20.70±7.9</td>
<td>22.10±7.3</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>13.40±3.3</td>
<td>12.90±3.6</td>
<td>13.50±2.8</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>357.40±63.3</td>
<td>541.20±82.7</td>
<td>355.50±71.7</td>
</tr>
<tr>
<td>Dr. bil (µmol/L)</td>
<td>0.15±0.07</td>
<td>0.17±0.08</td>
<td>0.16±0.09</td>
</tr>
<tr>
<td>T. bil (µmol/L)</td>
<td>1.01±1.4</td>
<td>0.61±0.2</td>
<td>1.06±1.7</td>
</tr>
</tbody>
</table>

*p>0.05. All values are expressed as mean± standard deviation; NS: not significant.
AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, LDH: lactate dehydrogenase, Dr. bil: direct bilirubin, T. bil: total bilirubin.

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**Figure 2** Serum homocysteine concentrations before anesthesia and after low-flow anesthesia. The mean (dotted line), median, 25th–75th percentiles (box boundaries) and 10th–90th percentiles (whiskers) are shown. Outliers beyond 10%–90% are shown as individual data points. There were no significant differences between the anesthetic groups.
result in hepatic and renal damage. Nephro-
lites of sevo flurane and breakdown products from its

desflurane or sevoflurane. On the contrary, metabo-

ly preserved in elderly patients anesthetized with

Suttner et al. (14) showed that hepatic function was

ly reduced at high concentrations over 8.3% (13).

Armbruster et al. reported that desflurane caused a
dose-dependent decrease in hepatic arterial blood

flow in a pig model. However, it did not change
hepatic metabolic functions significantly, although O2

delivery to the whole body and the liver was marked-

ly reduced at high concentrations over 8.3% (13).

(29) showed that general anesthe-

sis with desflurane did not aggravate renal impair-

ment in patients with preexisting renal insuffi-

ency. Several studies have shown that sevoflurane anesthe-

sia in open surgery at various fresh gas rates (1–4.4

L/min) was found to be safe in patients with normal

renal function (15, 30). To our knowledge, sevoflu-

rane anesthesia can cause transient dysfunction of

several parts of the human nephron. Albuminuria and

slightly greater proteinuria indicate glomerular injury

(6). Therefore, it has been suggested that low-flow

sevoflurane anesthesia (<1 L/min) would not be safe

in patients with renal impairment (4). Patients with

preexisting renal disease are at an increased risk for

further postoperative deterioration of function and

CpA nephrotoxicity may add to this risk. Eger et al.

found that renal injury, as defined by postoperative

concentrating defects and increased urinary levels of

N-acetyl-b-glucosaminidase, correlated with increased

inorganic fluoride levels produced by sevoflurane

biodegradation (6). Although CpA was shown to exhi-

bit nephrotoxicity in rodents, no significant changes in

renal function parameters were reported in surgical

patients (5, 26, 31, 32). In a previous study, it was

reported that plasma inorganic fluoride concentra-
tions were regularly increased after sevoflurane anes-

thesia and were not associated with nephrotoxicity.

Histological examination in horses revealed that sevo-

flurane anesthesia was associated with mild micro-

scopic changes in the kidney involving mainly the dis-
tal tubule, but no remarkable alterations in hepatic

tissue. These results indicate that horses can be main-
in a systemically healthy state during unusual-
ly prolonged sevoflurane anesthesia with minimal risk

of hepatocellular damage from this anesthetic (12, 26).

In human studies, sevoflurane and desflurane were

found to have no adverse hepatic effects (33). It

was also suggested that desflurane was a safe agent
even in patients with chronic hepatic and renal dis-

ese (34). In our study, we also did not find any

deterioration in hepatic functions. It was shown that

pneumoperitoneum of 10 mmHg, resulting from the

laparoscopic surgery technique, caused a 70% de-

crease in GFR (32). It was also suggested that the

pneumoperitoneum reduced the hepatic portal blood

flow, although it did not alter the clinically important

postoperative hepatic transaminases (35–37). In

these patients, selection of the anesthetic agent,

which has minimal or no effect on renal and hepatic

functions, and a low fresh gas flow rate are very

important. CO2 insufflated during the pneumoperi-
toneum period is absorbed into circulation, which

may cause many side effects. During low-flow anes-

thesia reduced CO2 is produced due to lower meta-

bolism of the anesthetic agent. Thus, low-flow anes-

thesia may minimize the total amount of CO2 in the

pneumoperitoneum by reducing gas consumption

resulting from anesthetic agent metabolism (3–37).

In conclusion, we demonstrated that low-flow

sevoflurane and desflurane anesthesia did not impair

renal and hepatic functions. Sevoflurane has more pro-
tective effects than desflurane that result in de crea sed

morbidity and mortality. The present data show for the

first time that the choice of low flow anesthesia with

volatile anesthetics is associated with a better outcome

after laparoscopic surgery. In addition, low flow anes-

thesia did not affect the biochemical parameters and

may be a good alternative to the conventional high-

flow anesthesia techniques. We showed that creatinine

clearance and homocysteine are important diagnostic

biomarkers for renal metabolic function. Further stu-
dies are required to assess in terms of biochemical

parameters or new diagnostic markers the other po-
tential advantages of low-flow techniques, with parti-
cular regard to economic considerations.

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Conflict of interest statement

The authors stated that there are no conflicts of

interest regarding the publication of this article.
References


