A comparison of renal responses to sevoflurane and isoflurane in patients undergoing donor nephrectomy: a randomized controlled trial

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Abstract

Sevoflurane and isoflurane are volatile halogenated ether widely used in anesthesia. Both have comparable potency and easy titratability but sevoflurane has lower pungency and results in faster patient recovery. Isoflurane, however, is more affordable. The nephrotoxicity of sevoflurane is undisputed but studies on isoflurane nephrotoxicity are lacking. The objective of this paper is to determine the overall nephrotoxicity profile of sevoflurane and isoflurane in donor nephrectomy patients using the renal function markers – nuclear glomerular filtration rate (GFR), serum creatinine, urine protein-to-creatinine ratio, proteinuria, and glucosuria. A randomized comparative study of postoperative renal functions in donor nephrectomy patients who had received either low-flow (< 1 L/min) sevoflurane or isoflurane were analyzed. The renal parameters were repeated 72 hours post anesthesia. Forty-seven subjects (46%) were randomized to receive isoflurane while fifty-five received sevoflurane (54%). Between the two anesthetic groups, there was no significant difference in terms of serum creatinine, total GFR, or nuclear GFR. There was a statistically higher proportion of patients with urine protein-to-creatinine ratios of 0.2 and above in the isoflurane group (64% *vs*. 38%), while more patients in the sevoflurane group had ratios above 0.2 (62% *vs*. 36%, $P < 0.05$). The type of anesthetic agent was not an independent predictor of increasing serum creatinine, total GFR and urine protein-to-creatinine ratio and nuclear GFR. In conclusion, the overall nephrotoxicity profile of sevoflurane and isoflurane-treated donor nephrectomy patients is minimal.

Key words: sevoflurane; isoflurane; nephrotoxicity; donor nephrectomy

doi: 10.4103/2045-9912.202906
How to cite this article: Ong Sio LCL, dela Cruz RGC, Bautista AF. A comparison of renal responses to sevoflurane and isoflurane in patients undergoing donor nephrectomy: a randomized controlled trial. Med Gas Res. 2017;7(1):19-27.
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Introduction

There has been widespread use of sevoflurane in clinical practice due to its affordability and unique pharmacokinetic properties. However, its nephrotoxic potential due to compound A (CpA) is concerning. Factors that are predisposed to increased CpA include low fresh gas flow, baralyme as absorbents, and high sevoflurane concentration.[1]

Sevoflurane is degraded to CpA by carbon dioxide absorbents containing strong base. Evidence suggests that relatively high concentrations of CpA could cause dose-dependent renal injury and death in rats but not in humans.[2] Necrosis was then found to be at the corticomedullary junction, primarily in proximal tubular cells within the outer strip of the outer medulla.[3] In a rat study performed by Keller et al.,[4] rats with minimal necrosis had no changes in serum chemistry or urine parameters indicative of impaired renal function, whereas in rats with moderate necrosis (10% to 30% affected tubule cells), more marked changes in the serum and urine parameters were observed.[4,5]

On the other hand, several studies have shown no statis-

tical difference in measured parameters of renal function in humans. Studies by Conzen et al.,[1] Higuchi et al.,[6] and Groudine et al.[7] have been the subjects of discourse since the parameters used (blood urea nitrogen or BUN, serum creatinine) are not sensitive indicators of renal impairment. Other studies utilizing albuminuria, glucosuria, and enzyme markers such as alpha-glutathione-S-transferase (GST) and pi-GST found in tubular injuries failed to predict the presence or absence of renal injury.[8]

There have been several literatures that looked into the nephrotoxic potential of sevoflurane in patients with renal insufficiency. In a study by Mcgrath et al.[9] on the effect of sevoflurane versus isoflurane on renal function in patients with renal insufficiency, they concluded that there was no clinically significant difference in serum creatinine concentrations measured pre- and post-operatively. A similar study done by Nuscheler et al.[10] among patients with renal impairment likewise showed no clinically significant change in serum creatinine concentrations.

In a study done by Higuchi et al.[6] on the comparison of low-flow and high-flow sevoflurane with isoflurane, the conclusions expressed that low-flow sevoflurane was associated with mild and transient proteinuria. Furthermore, there were no significant changes noted in BUN, creatinine, or creatinine clearance.

In a study by Kharasch et al.,[11] renal function after long-duration low-flow (< 1 L/min of fresh carrier gas) sevoflurane and isoflurane anesthesia was compared in surgical patients with normal renal function. Results showed that there was no significant difference between anesthetic groups in 24- or 72-hour serum creatinine, BUN, creatinine clearance, or 0- to 24-hour or 48- to 72-hour urinary protein or glucose excretion. Proteinuria and glucosuria were common in both groups. However, there was no correlation between CpA exposure and any renal function measure. There was no evidence of nephrotoxicity observed for low-flow sevoflurane, even at high CpA exposures. Proteinuria and glucosuria were common.

Tsukamoto et al.[12] studied the effects of sevoflurane and isoflurane anesthesia on renal tubular functions in 14 patients with moderately impaired renal function. Results showed that although both the peak plasma inorganic fluoride concentrations and the areas under the curve of plasma inorganic fluoride concentration versus time were significantly greater in the sevoflurane group than in the isoflurane group, urine N-acetyl-β-D-glucosaminidase (NAG), gamma-glutamyl transpeptidase, and β-2-microglobulin excretions per day did not differ between the two groups. These results proved that sevoflurane and isoflurane have similar effects on the renal tubules in patients with moderately impaired renal function.

Proteinuria is a hallmark of many renal disorders, and quantification of proteinuria helps the clinician determine if significant renal disease is present, and differentiate between glomerular diseases and tubulo-interstitial diseases. The standard method of measurement of urine protein excretion involves the determination of protein concentration in a timed urine collection. A 24-hour urine collection is typical. This is extremely useful in the clinical setting because it provides enough information to assess the degree of proteinuria and determine if heavy (nephrotic range) proteinuria is present. A ratio of < 0.1 is normal (protein and creatinine are in mg/dL). In general, a protein-to-creatinine ratio > 2.5 suggests the presence of nephrotic range proteinuria. Therefore, the urine protein-to-creatinine ratio is used to estimate the degree of proteinuria. Because the urine protein-to-creatinine ratio is fully quantitative, it can be used to monitor therapy. In fact, recent studies have shown that persistently high ratios are significantly correlated to poor prognoses.[12,13]

Conzen et al.[1] assessed 116 patients with renal insufficiency who had a stable preoperative serum creatinine concentration 1.5 mg/dL or greater. Renal function (serum creatinine and BUN, urine protein and glucose, creatinine clearance) was measured preoperatively and 24 and 72 hours after induction. Results showed that there were no statistically significant differences in measured parameters of renal function after low-flow sevoflurane anesthesia compared with isoflurane.

An unpublished meta-analysis done by Bautista[13] on sevoflurane and renal function included a total of 6 relevant clinical trials qualified for critical appraisal. A total pool of 873 patients was acquired with ages ranging from 19 to 67 (mean of 56 ± 3) years, with 557 males and 316 females, without co-existing hepato-renal dysfunction and underwent elective surgery ranging from 2.5 hours to 5 hours. Low-flow sevoflurane and low-flow isoflurane were the main comparisons although two studies included a high-flow arm. All studies were comparable in terms of patient profile and techniques of anesthesia administration, anesthesia time, and duration of surgery. All individual studies had values of creatinine within normal range at 24, 48 and 72 hours for both groups. Using a random-effects model, no significant difference in the standard mean difference for creatinine values was noted between sevoflurane and isoflurane at 24 and 72 hours post-anesthesia. Likewise, BUN did not vary significantly between the two arms for 24 and 72 hours.

The utilization of nuclear glomerular filtration rate (GFR) has not been described in literature as a potential tool to assess renal impairment in patient who had sevoflurane. GFR is defined as the rate (volume per unit of time) at

which ultra-filtrate is formed by the glomerulus. It is a direct measure of renal function and is related to the severity of the structural abnormalities in chronic renal disease.[14] GFR is conventionally corrected for body surface area, and the normal value is approximately 1.73 m^2. A normal range can be derived to assess renal impairment when corrected for body surface area. The normal corrected GFR is 80–120 mL/min/1.73 m^2. Impaired renal function is defined as GFR of 30–80 mL/min/1.73 m^2. Corrected GFR is 8% lower in women than in men, and declines with age.

This study aimed to use nuclear GFR, serum creatinine, urine protein-to-creatinine ratio, glucosuria, and albuminuria as parameters in measuring and comparing renal dysfunction caused by sevoflurane and isoflurane in donor nephrectomy patients.

Subjects and Methods

Study design

This study was designed as a randomized controlled comparative evaluation of post-operative renal functions of patients who underwent donor nephrectomy and received low flow (≤1 L flow) sevoflurane and isoflurane.

Study participants

Approval from the National Kidney and Transplant Institute Ethics Committee in Manila, Philippines was secured and written informed consent was taken prior to the enrollment in the study.

Patients who came for elective donor nephrectomy were recruited. Inclusion criteria were patients with American Society of Anesthesiologists (ASA) classification I & II for donor nephrectomy, adults aged 18 to 45 years, with no history of renal impairment, normal renal function as measured by nuclear GFR and serum creatinine, negative for glucose and protein in urinalysis. Patients were excluded from the study if there was a note of previous unusual response to a halogenated anesthetic and use of contrast media 24 hours before and after surgery. The same size (n = 102) was calculated to reject the null hypothesis yielding a study power of 80% to detect a 10% difference in renal failure rate between the two groups and pegged at a α level of significance.

Randomization

Randomization was done using www.randomization.com. A computer-generated randomization was done and patients were assigned to groups as they get enrolled in the study. Investigators did not know which inhalational drug each patient would receive until enrollment and random assignment to sevoflurane and isoflurane groups. Unblinding of data occurred only after data analysis was completed.

Intervention

Preoperative visit

Patients were advised to fast post-midnight and anesthetic plan was explained (general endotracheal anesthesia). Preoperative GFR, serum creatinine, urinary albumin and glucose were noted. Intravenous fluid using Lactated Ringer's solution in 5% dextrose was started and infused initially at an hourly-maintenance rate based on the patient's weight. A standard preoperative medication regimen for all patients consisting of nalbuphine 0.2 mg/kg and diphenhydramine 50 mg was given intramuscularly one hour prior to the contemplated procedure.

Preinduction

Standard monitoring devices, which included automated non-invasive blood pressure, electrocardiogram (EKG), oxygen saturation and end-tidal partial pressure of carbon dioxide ($PETCO_2$) were hooked to the patient. After written informed consent, patients were randomized to receive either low-flow sevoflurane or isoflurane.

Induction and maintenance

After breathing 100% oxygen for 3 minutes, anesthesia was induced with propofol 1% at 1.5–2.5 mg/kg intravenously and fentanyl 1.0 μg/kg. Rocuronium at 0.6 mg/kg intravenous injection was given to facilitate endotracheal intubation. Thereafter, ULTANE® (sevoflurane) volatile liquid for inhalation Novaplus™ and FORANE (isoflurane, USP) were given at a total fresh gas flow of ≤ 1 L/min. The lungs were ventilated using intermittent positive pressure ventilation. The ventilation pattern was maintained with a respiratory rate of 12–15 breaths per minute at a tidal volume of 8 mL/kg and $PETCO_2$ using capnography between 35–40 mmHg (1 mmHg = 0.133 kPa).

Emergence

At the end of the surgery, the absence of a clinically relevant neuromuscular blockade was confirmed with a nerve stimulator, the vaporizer was turned off, and fresh gas flow was increased to 6 L/min oxygen.

Laboratory examinations were done at least within 48 hours prior to the operation, which included serum creatinine, urinalysis, and urine protein-to-creatinine ratio. The nuclear GFR was done within 1 month preoperatively. Nuclear GFR, blood and urine samples were obtained 72 hours post-anesthesia.

Outcome measures

The primary outcome measure was 10% decrease in nuclear glomerular filtration rate. All hemodynamic parameters, oxygen saturation, $PETCO_2$ plus the inspired and end-tidal

sevoflurane and isoflurane concentrations were monitored continuously and recorded every 2 minutes after intubation until surgical incision and every 5 minutes thereafter until extubation.

The minimum alveolar concentration (MAC) hour exposure was calculated from the percent anesthetic concentration and the duration of exposure. MAC values were corrected for age using the following equation: MAC corrected = (A) × (10^{B}) × (X), in which A is MAC at 40 years (2% sevoflurane, 1.17% for isoflurane), B is –0.00269, X is the difference from age 40 years.

$$\text{MAC hour} = \frac{(\text{ET concentration}) \times (\text{duration of anesthesia})}{\text{MAC corrected}}$$

The resultant values were recorded as the MAC hour.

Statistical analysis

Statistical analyses were done using GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA) and Statistical Package for the Social Sciences (SPSS Version 14, SPSS, Chicago IL, USA). Descriptive statistics included mean and standard deviation for continuous numerical variables while percentage frequency distribution was utilized for categorical data. Testing for sample homogeneity was done using independent *T*-test for continuous data and chi-square for categorical data. Within groups, comparison was done using paired *t*-test while between groups comparison was performed using independent *T*-test. Regression analysis using stepwise technique was utilized to determine the relationship of clinical factors with renal function post-exposure. Regression coefficients close to 1 or –1 with *P*-values less than 1 are considered significant predictors of outcome. All tests of significance were carried out at a significant level of $\alpha = 0.05$.

Results

Baseline clinical profile

A total of 102 kidney donors met the inclusion criteria. Forty-seven subjects (46%) were randomized to receive isoflurane while fifty-five received sevoflurane (54%). This sample was sufficient to reject the null hypothesis that the post-exposure renal function outcomes did not significantly differ between the two anesthetic agents. Our study had more than 90% of retrospective power to detect a 20% difference in creatinine and GFR levels between the groups. The baseline clinical profile is summarized (**Table 1**). Most subjects were in the third decade of life. There was no statistically significant difference between the two groups in terms of age ($P = 0.21$), weight ($P = 0.71$), nephrectomy procedure ($P = 0.21$) and ASA classification ($P = 0.19$). Percentage-wise, there were more male subjects in the sevoflurane group (74%) than in the isoflurane group (51%) ($P < 0.05$), which was statistically significant.

At baseline pre-exposure state, serum creatinine were comparable between the two groups (isoflurane: mean 0.93 ± 0.13 *vs*. 1.08 ± 1.1 sevoflurane, $P = 0.21$), as well as the total nuclear GFR (mean = 100.1 ± 9.3 *vs*. 97.4 ± 10.1, $P = 0.17$). However, the baseline nuclear GFR was statistically higher among those who were randomized to isoflurane when compared to sevoflurane in both the left and right kidneys (left kidney, isoflurane = 50.6 ± 5.2 *vs*. 47.8 ± 7.2, $P < 0.05$ and right kidney = 50.4 ± 5.4 *vs*. 47.3 ± 5.5, $P < 0.05$). A slightly higher percentage of patients in the sevoflurane group had urine protein-to-creatinine ratios of 0.1 (78% *vs*. 68%, $P = 0.25$) while more patients in the isoflurane group had ratios of 0.2 (32% *vs*. 22%); however these proportions were not statistically significant ($P = 0.25$). In both groups, no patient had glucosuria or proteinuria (**Table 1**).

Anesthesia parameters and operative time

The concentrations of anesthesia significantly differed between the two groups ($P < 0.05$) (**Table 2**). The duration of surgery was slightly longer for the Isoflurane group compared with sevoflurane group (2.7 ± 0.77 hours *vs*. 2.47 ± 0.66 hours, $P = 0.06$) but the duration of anesthesia were comparable (3 ± 0.81 hours *vs*. 2.8 ± 0.76 hours, $P = 0.22$). Urine output was significantly lower in the isoflurane group (2.04 ± 1.01 mL/kg/h *vs*. 2.78 ± 1.11 mL/kg/h, $P < 0.05$).

Mean time of exposure to the inhalational anesthetics (MAC hours) for both groups was comparable (3.97 ± 1.8 *vs*. 3.87 ± 1.0) ($P = 0.74$). Likewise, the total intravenous fluids administered did not significantly vary (3.15 ± 0.75 *vs*. 3.18 ± 0.63, $P = 0.82$; **Table 2**).

Pre-exposure and post-exposure renal function using the two anesthetic agents

A comparison of the different renal function parameters at pre-anesthetic exposure and post-exposure was done (**Table 3**).

Serum creatinine statistically increased with the isoflurane group (mean difference = –0.35, change = –26%, $P < 0.05$) but not in the sevoflurane group (mean difference = –0.28, change = –26%, $P = 0.068$).

In both groups, the total nuclear GFR significantly decreased. However, GFR per kidney statistically increased from the pre-exposure values ($P < 0.05$). In the left kidney, the percent increase in GFR was higher in the sevoflurane group *versus* the isoflurane group (mean difference = –5.9, change = –12.3%, $P < 0.05$ *vs*. mean difference = –4.5, change = –8.9% respectively). In the right kidney, the percent increase from baseline GFR was higher in the isoflurane *versus* the sevoflurane group (mean difference = –11.7, change = –23.2%, $P < 0.05$ *vs*. mean difference =

Table 1: Baseline profile of kidney donors randomized to isoflurane versus sevoflurane anesthesia for donor nephrectomy

Characteristic	Isoflurane (*n*=47)	Sevoflurane (*n*=55)	*P*-value
Age (years)			
Mean±SD	30.7±5.5	29±7.4	0.20*
Range	22–47	20–50	
Sex			
Male	24 (51)	41 (74)	< 0.05+
Female	23 (49)	14 (26)	
Weight (kg)			
Mean±SD	59.3±12.7	57.8±11.2	0.80*
Range	36–90	42–78	
American Society of Anesthesiologists (ASA) classification			
I	35 (75)	47 (85)	0.21+
II	12 (25)	8 (15)	
Serum creatinine (μM)			
Mean±SD	41 (87)	52 (95)	0.30+
Range	6 (13)	3 (5)	
Total glomerular filtration rate			
Mean±SD	0.93±0.13	1.08±1.1	0.34*
Range	0.7–1.2	0.7–9.0	
Pre-operative nuclear glomerular filtration rate			< 0.05*
Left kidney	50.6±5.2	47.8±7.2	< 0.05+
Right kidney	50.4±5.4	47.3±5.5	
Urine protein-to-creatinine ratio			0.27*
0.1	32 (68)	43 (78)	
0.2	15 (32)	12 (22)	
Urine albumin			–
Positive	0	0	
Negative	47 (100)	55 (100)	
Urine glucose			–
Positive	0	0	
Negative	47 (100)	55 (100)	

Note: Categorical data were expressed as *n* (%). * indicates comparison using independent *T*-test comparison; + indicates comparison using chi-square test.

–7.8, change = –16.4%, $P < 0.05$).

The urine protein-to-creatinine ratios were significantly different in both groups post-exposure. In both groups, more patients had significantly increased urine protein-to-creatinine ratios post-exposure. In the isoflurane group, an increase in the ratio of 0.2 was noted (baseline = 32% to 64%) and ratios of > 0.2 (baseline = 0 to 36%). However, those with a ratio of 0.1 dropped during the post-exposure state (68% to 0). Likewise, in the sevoflurane group, an increase in the ratio of 0.2 was noted (baseline = 22% to 38%), ratio of > 0.2 (baseline = 0 to 62%). A drop in the proportion of subjects with ratios of 0.1 was noted (baseline = 78% to 0% at post-exposure). No patient developed glucosuria and or proteinuria post-exposure.

Table 2: Anesthesia parameters and operative time of kidney donors

Characteristic	Isoflurane (*n*=47)	Sevoflurane (*n*=55)	*P*-value
Concentration delivered (%)			
Mean±SD	1.36±0.32	2.3±0.32	0.05
Range	0.7–2.0	1.3–2.8	
Duration of surgery (hours)			
Mean±SD	2.7±0.77	2.47±0.66	0.06
Range	2–5	2–4	
Duration of anesthesia (hours)			
Mean±SD	3±0.81	2.8±0.76	0.22
Range	2–5	1–4	
Intravenous fluids (L)			
Mean±SD	3.15±0.75	3.18±0.63	0.82
Range	2–4.6	2–4.5	
Minimum alveolar concentration hour exposure			
Mean±SD	3.97±1.8	3.87±1.0	0.74
Range	1.4 –10.55	1.95–7.7	
Mean arterial pressure (mmHg)			
Mean±SD	81.2±8.7	79.7±11	0.46
Range	66.7–97	53.3–95.3	
Urine output (mL/kg/hour)			
Mean±SD	2.04±1.01	2.78±1.11	0.05
Range	0.5–4.6	1.2–6.84	

Note: Intergroup comparison was performed through independent *T*-test.

Comparison of the effects of isoflurane *versus* sevoflurane on renal function

At post-exposure state, the two groups of anesthetic agents did not statistically differ in terms of serum creatinine ($P = 0.11$), total GFR ($P = 0.14$), post-exposure nuclear GFR in the right kidney ($P = 0.59$) and left kidney ($P = 0.08$).

A statistically higher percentage of patients with protein-to-creatinine ratios of above 0.2 was noted in the sevoflurane group (62% *vs*. 36%, $P < 0.05$; **Table 4**).

Logistic regression analysis of the factors affecting post-operative renal functions between the isoflurane and sevoflurane groups

Table 5 summarizes the clinical factors that affected the

Table 3: Baseline profile of kidney donors randomized to isoflurane *versus* sevoflurane anesthesia for donor nephrectomy

Item	Pre-exposure	Post-exposure	Mean difference	Percent change from baseline (%)	*P*-value
Serum creatinine (μM)					
Isoflurane	0.93±0.13	1.28±0.26	–0.35	–37.6	< 0.05*
Sevoflurane	1.08 ± 1.1	1.36±0.25	–0.28	–26.0	0.09*
Total glomerular filtration rate					
Isoflurane	100.1±9.3	58.8±11.2	41.3	41.2	< 0.05*
Sevoflurane	97.4±10.4	55.3±12.4	42.1	43.2	< 0.05*
Nuclear glomerular filtration rate					
Left kidney					
Isoflurane	50.6±5.2	55.1±9.7	–4.5	–8.9	< 0.05*
Sevoflurane	47.8±7.2	53.7±9.5	–5.9	–12.3	
Right kidney					< 0.05+
Isoflurane	50.4±5.4	62.1±9.1	–11.7	–23.2	< 0.05*
Sevoflurane	47.3±5.5	55.1±15.2	–7.8	–16.4	< 0.05+
Urine protein-to-creatinine ratio					
Isoflurane					< 0.05*
0.1	32 (68)	0	–	–	
0.2	15 (32)	30 (64)			
> 0.2	0	17 (36)			
Sevoflurane			–	–	< 0.05*
0.1	43 (78)	0			
0.2	12 (22)	21 (38)			
> 0.2	0	34 (62)			
Urine albumin positive					
Isoflurane	0	0	–	–	–
Sevoflurane	0	0			
Urine glucose positive					
Isoflurane	0	0	–	–	–
Sevoflurane	0	0			

Note: Percent change from baseline (%) = (pre-operative – post-operative)/pre-operative × 100%. Negative results (–) indicate lesser values at baseline.

post-exposure nuclear GFR. The more prolonged the anesthesia, the GFR drops correspondingly. (β = –0.354, 95%*CI* –10.58, –0.037) while an increase in the pre-exposure GFR in the left kidney results to a drop in total GFR (β = 0.328, 95%*CI* 0.053, 1.15). Lastly, the baseline urine protein-to-creatinine ratio is a significant predictor of post-exposure GFR. (β = –0.446, 95%*CI* –177.22 to – 62.98). The type of anesthetic agent was not a significant factor (**Table 5**).

Post-exposure serum creatinine levels

Post-exposure serum creatinine is highly impacted by patient weight and fluid requirements (β = 0.553, 95%*CI* 0.006 – 0.019, $P < 0.05$; β = –1.53, 95%*CI* –0.195, –0.031, $P < 0.05$).

Urine protein-to-creatinine ratio

Post-exposure urine protein-to-creatinine ratio is only impacted by the ratio obtained at baseline (β = 1.84, 95%*CI* 1.21–2.48, $P < 0.05$). The rest of the factors were not predictive.

Nuclear GFR per kidney

In both the right and left kidneys, there were no significant predictors of a decrease in GFR identified. The type of anesthetic agent was, again, not an independent predictor of this outcome.

Discussion

Dispute regarding the effect of sevoflurane on perioperative renal functions continues. In this study, we compared the renal responses of donor nephrectomy patients who used either low-flow sevoflurane or isoflurane, and found no compelling difference in nephrotoxic potential between sevoflurane and isoflurane.

Table 4: Comparative effects of isoflurane and sevoflurane on renal function at post-operative state

Characteristic	Isoflurane (*n*=47)	Sevoflurane (*n*=55)	*P*-value
Serum creatinine (μM)			
Mean±SD	1.28±0.26	1.36±0.25	0.11
Total nuclear glomerular filtration rate			
Mean±SD	58.8±11.2	55.3±12.4	0.14
Nuclear glomerular filtration rate			
Left Kidney	55.1±9.7	53.7±9.5	0.59
Right Kidney	62.1±9.5	55.1±15.2	0.08
Urine protein-to-creatinine ratio			
0.1	0	0	–
0.2	30 (64)	21 (38)	< 0.05
> 0.2	17 (36)	34 (62)	< 0.05
Urine albumin			
Positive	0	0	–
Negative	47 (100)	55 (100)	–
Urine glucose			
Positive	0	0	–
Negative	47 (100)	55 (100)	–

The nephrotoxic potential of sevoflurane is attributed to the formation of CpA.[3] Making the most of exposure to CpA is done by limiting fresh gas flow to ≤ 1 L/min. The lower flows minimize CpA removal from the breathing circuit mandating more CO_2 to be removed by the circuit's absorber system.[7] This exothermic reaction can increase the temperature of the absorber and result in higher CpA production. The production of CpA increases 2.5-fold when the temperature is increased from 26°C to 46°C.[5,7] CpA production is also directly proportional to the concentration of sevoflurane.[5,15] The concentration of sevoflurane used was noted to be at 2.3 ± 0.32%. The amount of time spent at low-flow anesthesia has the effect of increasing CpA concentrations for the first 2 hours, after which the level plateaus. In this study, the mean duration of exposure to sevoflurane was 2.8 ± 0.76 MAC hours. Frink et al.[15] measured a decrease in the production of CpA after 2 hours and a fall in CpA levels after 4 hours, hence the reason the authors did not measure CpA levels in the study.

Nuclear GFR was used as one of the parameters for renal function. It was found to have 93% sensitivity and 94% specificity in detecting renal impairment.[15] The fall in total GFR post-operatively can be explained by the impact of unilateral nephrectomy. On the other hand, comparison of

Table 5: Regression analysis of factors associated with post-exposure nuclear glomerular filtration rate

Factor	Standardized regression coefficient	95%*CI*		*P*-value*	Comment
		Lower	Upper		
Age	0.381	–0.027	0.790	0.07	NS
Sex	1.619	–5.07	8.30	0.63	NS
Weight	–6.691E-02	–0.395	0.262	0.69	NS
Type of procedure	1.897	–4.99	8.78	0.59	NS
Type of anesthesia	–7.079	–17.47	3.32	0.18	NS
Concentration	5.060	–4.98	15.10	0.32	NS
American Society of Anesthesiologists (ASA) Classification	0.852	–9.31	11.01	0.87	NS
Duration of surgery	2.256	–4.45	8.97	0.54	NS
Duration of anesthesia	–5.361	–10.68	–0.037	< 0.05	Predictor
Average Mean arterial pressure	4.710E-02	–0.233	0.327	0.74	NS
Fluid volume	2.871	–1.28	7.03	0.17	NS
Minimum alveolar concentration hour-exposure	0.466	–2.64	3.57	0.77	NS
Pre-exposure creatinine	4.195E-02	–2.78	2.86	0.98	NS
Pre-exposure total glomerular filtration rate	–0.143	–0.558	0.273	0.50	NS
Pre-exposure glomerular filtration rate, left kidney	0.603	0.053	1.15	< 0.05	Predictor
Pre-exposure glomerular filtration rate, right kidney	0.141	–0.378	0.660	0.591	NS
Urine protein-to-creatinine ratio	–120.103	–177.22	–62.98	< 0.05	Predictor
Constant	33.21	–4.3	70.7	0.082	–

Note: *Significant association if regression coefficient is close to 1 or – 1 and *P*-value is < 0.05 (linear regression analysis). NS: Not significant.

the remaining kidney with its preoperative value showed an increase in GFR. This validates the findings that the mean renal volume of the remaining kidney is increased by roughly 15% compared to the preoperative values.[16,17] This could be explained by cellular hypertrophy and hyperplasia mainly of the proximal convoluted tubules. This concept is supported by the study using lithium clearance for the assessment of salt and water reabsorption by proximal tubules.[16] It was concluded that the ability of the tubules to increase reabsorptive power represents compensatory hypertrophy of the nephrons. Likewise, the secretory capacity of the proximal tubules had increased up to 75% of the preoperative levels 6 months after unilateral nephrectomy in human kidney donors.[16] Still, comparison between the sevoflurane and isoflurane group showed no statistical difference hence the aforementioned results are innate effects of the surgery itself and not due to the inhalational agents given.

Because of their availability in clinical chemistry laboratories and ease of measurement, BUN and creatinine have been widely used as routine markers to depict abnormalities in renal function. However, in the study by Isles and Peterson,[14] BUN has been shown to be less reliable a marker and results have been shown to correlate with other variables aside from renal function in comparison with creatinine. Thus, it is for the aforementioned reason why our analysis only included creatinine. Clinical renal function scales/scores utilize creatinine level change to diagnose renal failure and injury. Though there was an increase in the post-operative value which may be attributed as impact of unilateral nephrectomy on the renal function and volume of the remaining kidney[17]; results have shown that exposure to both sevoflurane and isoflurane showed no significant difference in serum creatinine post-operatively upon exposure to both inhalational anesthetics. This finding validated the effect on creatinine from previous studies.[1,6,7,18,19]

In rats, proteinuria and glucosuria are more sensitive indicators of CpA related nephrotoxicity than of BUN and creatinine.[4,8] Hence, the incidence of proteinuria and glucosuria upon exposure to low flow sevoflurane and low flow isoflurane has been included in this study. Proteinuria suggests glomerular injury whereas glucosuria is indicative of proximal tubular injury. Previous studies that have demonstrated transient appearances of these two may be suggestive of a probable renal injury.[20] However, this study showed absence of proteinuria and glucosuria in patients exposed to both sevoflurane and isoflurane.

Protein-to-creatinine ratio was also utilized in this study to monitor renal impairment. This examination correlates with glomerular function and predicts progression of renal diseases. This parameter is easier to perform, inexpensive, and less time consuming for the patient. This may be of major relevance when large populations must be screened for urinary proteins or when patients are expected to provide urine samples imprecisely collected, or both.[21] In this study, the post-exposure protein-to-creatinine ratio did not increase to an alarming level. Long term follow-up is advised.

There are a gamut of factors associated with surgery and anesthesia that have been pointed out as culprits in the development of renal impairment.[19] Antibiotics, surgical stress, preexisting renal disease, intraoperative blood pressure, site of surgery, and choice of anesthetics to name a few of implicated factors. Ebert et. al.[19,22] however, concluded that the clinical use of approximately 1 MAC sevoflurane in a FGF of only 1 L/min for procedures ranging from 3 to 10 hours did not have clinically significant adverse effects on renal function. Likewise proteinuria, albuminuria, and glucosuria levels were similar after operations with sevoflurane and the comparator group. There were no associations between intraoperative blood pressure, length of surgery, or anesthetic concentration and abnormal renal findings. These data indicate that probable non-anesthetic factors are primary determinants of renal impairment.

Conclusion

The results of our study show that sevoflurane and isoflurane has no overall difference in effect on the renal functions of donor nephrectomy patients.

Recommendations

Although, the above studies showed the relatively safe effects of the two anesthetic agents immediately post-anesthetic exposure, serial monitoring in terms of the serum creatinine, total GFR, nuclear GFR, and urine protein-to-creatinine ratios, urine albumin and glucose must be assessed several hours post-operatively. The anticipated nephrotoxic potential of these agents must be taken into consideration for kidney donors who undergo pre-operative evaluation and must be exhaustively assessed, including a carefully analyzed nuclear GFR for each kidney. Although no major changes in renal functions were reported between the two inhalational anesthetic agent groups in this study, we need to mention that our study assessed the short-term renal outcomes only.

Acknowledgments

Thanks to Ernesto Castillo and Jaime Velasquez from Department of Anesthesiology, National Kidney and Transplant Institute, Quezon City, Philippines, and Ozan Akca from Department of Anesthesiology and Perioperative Medicine, University of Louisville Louisville, KY, USA

Author contributions

All authors have made significant contributions in the

formulation of study concept and design and gathering of related literature; writing and editing the manuscript; and analysis and interpretation of data. All authors aproved and read the final version of this manuscript for publication.

Conflicts of interest

There are no conflicts of interest for all authors.

Plagiarism check

This paper was screened twice using CrossCheck to verify originality before publication.

Peer review

This paper was double-blinded and stringently reviewed by international expert reviewers.

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