Original Article

Incidence of Postoperative Renal Injury after Receiving Different Exposure of Low-Flow Sevoflurane in General Anesthesia

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Objective: To compare postoperative renal injury in low-flow sevoflurane anesthesia between more and less than two MAC-hours, and to determine the potential predisposing factors of postoperative renal injury.

Materials and Methods: The present study was a retrospective cohort study that included 400 patients who underwent low-flow general anesthesia with sevoflurane, determining maintenance of fresh gas flow not exceeding one liter per minute. All subjects were classified into two groups, those exceeding two MAC-hours and those receiving less than two MAC-hours. The diagnosis of postoperative renal injury followed the Kidney Disease Improving Global Outcomes criteria. The multivariable logistic regression analysis was performed to identify independent risk factors for postoperative acute kidney injury.

Results: The incidences of postoperative acute kidney injury among the patients received more and less than two MAC-hours groups were 20.1% and 21.5%, respectively (p=0.876). Factors found to be associated with postoperative acute kidney injury were ASA classification 2 (adjusted OR 7.82, 95% CI 1.0 to 59.2), ASA physical status 3 or higher (adjusted OR 9.85 95% CI 1.3 to 76.4), and obesity (adjusted OR 5.74, 95% CI 2.0 to 16.4). Exposure to low-flow sevoflurane for more than two MAC-hours was not associated with postoperative renal injury (adjusted odds ratio 0.89, 95% CI 0.5 to 1.5, p=0.666).

Conclusion: Exposure to low-flow sevoflurane exceeding two MAC-hours did not increase the risk of postoperative acute kidney injury.

Keywords: Acute kidney injury; Low flow general anesthesia; Sevoflurane

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Since 1952[1], the low-flow general anesthesia technique has proven its benefit as providing ecological advantages[2], the reduction of pollution[3,4], and the prevention of airway desiccation[5]. However, the United States Food and Drug Administration (FDA) has not approved the clinical use of low-flow sevoflurane exceeding two minimal alveolar concentration-hours (MAC-hours)[6] due to acute kidney injury (AKI) in experimental animals[7]. A recent meta-analysis of 41 randomized controlled trials concluded that fluoride and compound A from sevoflurane had no significant clinical findings as creatinine, creatinine clearance, and baseline renal function were comparable with alternative anesthetics. However, that study was not specific to low-flow anesthesia[8].

Additionally, the previous studies employed the Kidney Disease Improving Global Outcomes (KDIGO) serum criteria for AKI diagnosis and omitted urine output (UO) criteria because the data was usually lacking. An advantage of UO over serum creatinine (sCr) is the speed of the response. Therefore, this practice might cast an underestimation AKI diagnosis[9]. The main objective of the present study was to compare the incidence of postoperative AKI between patients undergoing low-flow sevoflurane at more and less than two MAC-hours, implementing the KDIGO's UO and serum criteria. The authors hypothesized that there was no difference between the two groups.

Materials and Methods

The present study was a retrospective cohort

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Table 1. Diagnosis and staging of acute kidney injury[a]

Stage	Serum creatinine	Urine output
1	1.5 to 1.9 times baseline or ≥0.3 mg/dL increase	<0.5 ml $kg^{-1} \cdot hr^{-1}$ for 6-12 hours
2	2.0 to 2.9 times baseline	<0.5 ml $kg^{-1} \cdot hr^{-1}$ for ≥ 12 hours
3	3.0 times baseline or increase in sCr to ≥4.0 mg/dL or initiation of renal replacement therapy or inpatients <18 years, decrease in eGFR to <35 mL/minute per 1.73 m^2	<0.3 ml $kg^{-1} \cdot hr^{-1}$ for ≥24 hours or anuria for ≥12 hours

sCr=serum creatinine

[a] Adapted with permission from the Kidney Disease Improving Global Outcome. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012;2[9]

study approved by the Human Research Ethics Committee (REC 62-438-8-1; Ref no. 3Jyzo-Keige-GGNyI-PT0E2-dhkgg), and was conducted in Songklanagarind Hospital, Prince of Songkla University, Thailand. The authors searched all anesthetic records between September and October 2019, from the Hospital Information System (HIS). The present study included patients over 18 years that underwent general anesthesia with low-flow sevoflurane indicating maintenance of fresh gas flow not exceeding one liter per minute. The choice of induction agents, opioids, and neuromuscular blocking agents depended on the anesthesiologists in charge. The carbon dioxide absorbent in use was soda-lime. Exclusion criteria were patients with glomerular filtration rate (GFR) less than 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, renal surgeries, open cardiac surgeries, and organ transplant surgeries due to overt risks[10].

The authors reviewed the HIS database for baseline data, underlying disease, laboratory value, and nephrotoxic drug administration. The information collected were intraoperative hypotension, fluid balance, and end-tidal gas analysis manually. Total anesthetic exposure was calculated in the RStudio program as the product of end-tidal concentration and time, determined in thirty-minute intervals, expressed as MAC-hours. Relevant parameters for AKI diagnosis according to the KDIGO criteria were sCr, GFR, and UO (Table 1). The authors collected these data from the HIS for seven days after surgery. Absence or unreliability of UO was defined as missing data and excluded from the study. The authors searched through the progress notes and nurse notes to reevaluate any questionable data and adopted the listwise deletion method for all missing data.

The present manuscript adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies. The sample size equation was used to test two independent proportions (two-tailed test). The AKI incidence in patients receiving sevoflurane from the literature review was 11.2%[11]. There was no specific data regarding low-flow sevoflurane and AKI. The present study employed ratio (r)=1, alpha (α)=0.05, and beta (β)=0.20. The calculated sample size was 196 cases per group.

Statistical analysis

Data were analyzed using RStudio, Version 1.2.5019 (RStudio Inc). Continuous data presented as mean with standard deviation or median with interquartile range, and categorical data as proportion and percentage. For univariable analysis, a student t-test and a rank-sum test were applied for continuous variables, whereas chi-square or Fisher's exact test was applied for categorical variables. A p-value of less than 0.05 was statistically significant. The variables were collected with a p-value below 0.2 by univariable analysis. Established risk factors are diabetes mellitus[12,13], chronic liver disease[14], nephrotoxic agent[10,15], intraoperative hypotension[10,16,17], and blood loss[15]. The authors added the exposure of sevoflurane due to clinical interest. One variable retained in a set of variables with a correlation coefficient >0.9 to avoid multicollinearity. The discriminatory capacity of the model was investigated using an area under the receiver operating characteristics curve (AUC) analysis. The final version of the model included the American Society of Anesthesiologists (ASA) physical status, body mass index, and sevoflurane exposure.

Results

One thousand three hundred forty-four medical records were reviewed and 684 were eligible. The authors excluded 103 patients and dismissed 181 patients for missing data, resulting in 400 cases for data analysis. Baseline characteristics are in Table 2. The mean age, preoperative comorbidities, and renal status were comparable between the two groups. Sevoflurane exposure was 1.2 and 3.5 MAC-hours in each group (p<0.001). Patients from both

Table 2. Patient characteristics

	Sevoflurane exposure		p-value
	≤2 MAC-hours (n=177)	>2 MAC-hours (n=223)	
Sex: male; n (%)	68 (38.4)	80 (35.9)	0.675
Age (years); median (IQR)	47 (36.0, 59.0)	47 (38.5, 57.0)	0.943
Body mass index (kg/m^2); mean±SD	23.1±3.6	23.4±3.8	0.329
ASA classification; n (%)			0.755
ASA I	13 (7.4)	20 (9.0)	
ASA II	116 (65.5)	139 (62.3)	
ASA >III	48 (27.1)	64 (28.7)	
Type of surgery; n (%)			0.002*
Superficial procedure	28 (15.8)	17 (7.6)	
ENT procedure	6 (3.4)	9 (4.0)	
Major orthopedic surgery	14 (7.9)	42 (18.8)	
Vascular surgery	10 (5.6)	5 (2.2)	
Intraperitoneal surgery	89 (50.3)	112 (50.2)	
Intrathoracic surgery	14 (7.9)	10 (4.5)	
Intracranial surgery	16 (9.0)	28 (12.6)	
Emergency surgery; n (%)	59 (33.3)	41 (18.4)	<0.001*
Diabetes mellitus; n (%)	20 (11.3)	17 (7.6)	0.277
Hypertension; n (%)	39 (22.0)	46 (20.6)	0.827
Chronic liver disease; n (%)	8 (4.5)	11 (4.9)	1
Heart failure; n (%)	1 (0.6)	3 (1.3)	0.633
Creatinine (mg/dL); median (IQR)	0.7 (0.6, 0.8)	0.7 (0.6, 0.9)	0.859
GFR (mL·min^{-1}·1.73 m^{-2}); median (IQR)	103 (89.0, 116.5)	105 (90.0, 114.2)	0.838
Preoperative NSAIDs; n (%)	9 (5.1)	13 (5.8)	0.917
Preoperative contrast; n (%)	38 (21.5)	34 (15.2)	0.139
Operative time (minute); median (IQR)	70 (55.0, 95.0)	210 (157.0, 283.5)	<0.001*
Anesthetic time (minute); median (IQR)	115 (95.0, 135.0)	260 (205.0, 337.5)	<0.001*
Sevoflurane exposure (MAC-hours); median (IQR)	1.2 (0.9, 1.6)	3.5 (2.7, 4.7)	<0.001*
Estimated blood loss (mL); median (IQR)	30 (10.0, 100.0)	300 (100.0, 600.0)	<0.001*
Total fluid rate (mL/hr); median (IQR)	415.4 (300.0, 600.0)	438.6 (319.2, 616.8)	0.392
PRC transfusion (cases)\; n (%)	16 (9.0)	47 (21.1)	0.002*
Intraoperative urine rate (mL/kg/hour); median (IQR)	2 (1.4, 3.2)	1.8 (1.2, 2.7)	0.206
Intraoperative NSAIDs; n (%)	39 (22.0)	74 (33.2)	0.019*
Intraoperative contrast; n (%)	8 (4.5)	3 (1.3)	0.067
Intraoperative diuretics; n (%)	3 (1.7)	26 (11.7)	<0.001*
Intraoperative hypotension (cases); n (%)	91 (51.4)	119 (53.4)	0.774

ASA=American Society of Anesthesiologists; ENT=ear, nose, and throat; GFR=glomerular filtration rate; IQR=interquartile range; MAC=minimal alveolar concentration; NSAIDs=non-steroidal anti-inflammatory drugs; PRC=pack red cell; SD=standard deviation

* Statistical significance

groups received a comparable amount of total fluid infusion and produced comparable intraoperative urine rates.

Preoperative sCr and GFR presented in 95.8% of the patients, whereas 59.5% had postoperative value. The incidence of postoperative AKI among patients who received more, and less than two MAC-hours groups were 20.1% and 21.5%, respectively (Table 3). Figure 1 displayed the timing of post-operative AKI. During the first postoperative day, the incidence of AKI was significantly lower in patient receiving more than two MAC-hours of sevoflurane than in the other group (p=0.015). Notably, 83.1% of the diagnoses of the postoperative AKI were within 24 hours after surgery and only 16.9% stayed in oliguria for more than one day. The authors analyzed univariable and multivariable logistic regression to identify independent risk factors of postoperative

Table 3. Incidence of postoperative renal injury after low-flow sevoflurane exposure

	Sevoflurane exposure; n (%)		p-value
	≤2 MAC-hours (n=177)	>2 MAC-hours (n=223)	
AKI	38 (21.5)	45 (20.2)	0.876
Stage 1	29 (16.4)	36 (16.2)	
Stage 2	9 (5.1)	9 (4.0)	
Stage 3	0 (0.0)	0 (0.0)	

AKI=acute kidney injury; MAC=minimal alveolar concentration

AKI (Table 4, 5). Potential confounding factors with p-value below 0.2 were adjusted. The independent risk factors of postoperative AKI were ASA classification 2 (adjusted OR 7.82, 95% CI 1.0 to 59.2), ASA physical status 3 or higher (adjusted OR 9.85, 95% CI 1.3 to 76.4), and obesity (adjusted OR 5.74, 95% CI 2.0 to 16.4). Exposure to low-flow sevoflurane more than two MAC-hours was not a risk factor for postoperative AKI.

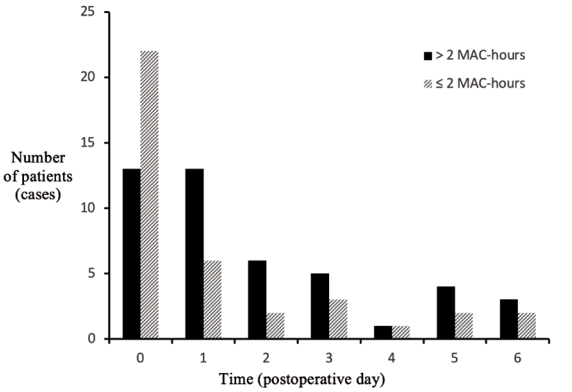

Figure 1. Number of patients who were diagnosed with postoperative acute kidney injury after low-flow sevoflurane anesthesia.

AKI=acute kidney injury; MAC=minimal alveolar concentration

Discussion

The incidence of postoperative AKI among patients receiving more and less than two MAC-hours was 20.1% and 21.5%, respectively (p=0.876). This amount is large compared with the previous retrospective reviews, which reported the incidence of 7.4% to 13.0%[11,18,19]. One possible explanation is that UO is more sensitive than sCr[9]. Therefore, we detected more cases. Another reason is that the present study covered high-risk patients, including emergency cases, prolonged surgery, and trauma. The last explanation could be the timing of diagnoses as the cases were detected within 24 hours after surgery, whereas only one-fifth stayed in oliguria for more than one day. Searching for postoperative AKI after this period possibly missed cases.

The authors did not assess other serum markers of kidney function because there is a broad consensus that changes in sCr or UO are the basis of all diagnostic criteria for AKI[9]. Intraoperative oliguria could be affected by hypovolemia, anesthetic agent, and hormonal responses to stress[20]. However, the present study presented the median intraoperative UO rate was about 1.9 mL/kg/hour.

The subsequent analysis displayed an exceptional result. The incidence of AKI in the first postoperative day was significantly lower in the group of sevoflurane exposure exceeding two MAC-hours (p=0.015). The possible mechanism could be from the pre-ischemic conditioning and renal protection effect. A former experiment demonstrated that the H_2O_2-mediated necrotic mechanism created anti-necrotic and anti-inflammatory effects in proximal renal tubules[21-24]. Additionally, sevoflurane reduced markers of inflammation by transcription of pro-inflammatory messenger ribonucleic and nuclear translocation of pro-inflammatory transcription factors[21,24].

The limitation of the present retrospective study was that postoperative sCr, and GFR were not routinely investigated, and only sixty percent of the patient had postoperative values. However, all positive cases with creatinine criteria were already diagnosed with UO criteria, affirming the sensitivity of AKI diagnosis with UO. UO documentation interpretation is challenging. The frequency and amount of urine were recorded in the nurse-note. If the patients did not have the Foley catheter, nursing assistants would measure UO in the bedpan or urinal bottle. The authors investigated through progress notes and nurse notes to dismiss false oliguria, including acute urinary retention, urine leakage, and fecal contamination. Additionally, specific patient characteristics had a shorter hospital stay than seven days, thus unable to have complete record.

The authors clinical recommendation is always measuring UO and sCr together for AKI diagnosis as sCr alone may miss cases. Special attention during the first postoperative day is notable. Future studies should include the effects of diuretics and fluid balance and the criteria modification for obese patients. Study in automatic gas control is valuable, for it is more economical[25].

Conclusion

The overall incidence of postoperative AKI in

Table 4. Univariable analysis of independent risk factors associated with postoperative acute kidney injury

	AKI (n=83)	No AKI (n=317)	p-value
Sex: male; n (%)	33 (39.8)	115 (36.3)	0.648
Age (years); median (IQR)	49 (39.0, 59.0)	47 (36.0, 58.0)	0.242
ASA classification; n (%)			0.023*
Class 1	1 (1.2)	32 (10.1)	
Class 2	54 (65.1)	201 (63.4)	
≥ Class 3	28 (33.7)	84 (26.5)	
Body mass index; n (%)			<0.001*
<18.5 (underweight)	4 (4.8)	38 (12.0)	
18.5 to 24.9 (normal)	52 (62.6)	190 (59.9)	
25 to 29.9 (overweight)	15 (18.1)	83 (26.2)	
≥30 (obese)	12 (14.5)	6 (1.9)	
Type of surgery; n (%)			0.815
Superficial procedure	7 (8.4)	38 (12.0)	
ENT procedure	4 (4.8)	11 (3.5)	
Major orthopedic surgery	12 (14.5)	44 (13.9)	
Vascular surgery	4 (4.8)	11 (3.5)	
Intraperitoneal surgery	41 (49.4)	160 (50.5)	
Intrathoracic surgery	7 (8.4)	17 (5.3)	
Intracranial surgery	8 (9.7)	36 (11.3)	
Emergency surgery; n (%)	20 (24.1)	80 (25.2)	0.943
Diabetes mellitus; n (%)	7 (8.4)	30 (9.5)	0.940
Hypertension; n (%)	22 (26.5)	63 (19.9)	0.244
Chronic liver disease; n (%)	5 (6.0)	14 (4.4)	0.563
Heart failure; n (%)	1 (1.2)	3 (0.9)	1.000
Creatinine (mg/dL); median (IQR)	0.7 (0.6, 0.9)	0.7 (0.6, 0.8)	0.040*
GFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$); median (IQR)	101 (88.0, 110.0)	105 (90.0, 116.8)	0.038*
Anemia; n (%)	16 (19.3)	44 (13.9)	0.298
Preoperative NSAIDs; n (%)	4 (4.8)	18 (5.7)	1.000
Intraoperative NSAIDs; n (%)	25 (30.1)	88 (27.8)	0.773
Postoperative NSAIDs; n (%)	31 (37.3)	159 (50.2)	0.050*
Preoperative contrast; n (%)	14 (16.9)	58 (18.3)	0.888
Intraoperative contrast; n (%)	4 (4.8)	7 (2.2)	0.250
Postoperative contrast; n (%)	11 (13.3)	27 (8.5)	0.271
Operative time (minute); median (IQR)	130 (75.0, 252.5)	141 (80.0, 215.0)	0.631
Anesthetic time (minute); median (IQR)	180 (120.0, 325.0)	190 (120.0, 265.0)	0.391
Estimated blood loss (mL); median (IQR)	100 (30.0, 400.0)	100 (20.0, 400.0)	0.809
Crystalloid rate (mL/hour); median (IQR)	357.4 (290.3, 497.8)	409.8 (291.2, 561.7)	0.033*
Total fluid rate (mL/hour); median (IQR)	403.4 (317.1, 559.5)	434.8 (311.4, 631.7)	0.226
PRC transfusion; n (%)	16 (19.3)	47 (14.8)	0.411
Urine output (mL/kg/hour); median (IQR)	1.9 (0.9, 2.7)	1.9 (1.2, 3.1)	0.331
Intraoperative hypotension; n (%)	43 (51.8)	167 (52.7)	0.985
Sevoflurane exposure >2 MAC-hours; n (%)	45 (54.2)	178 (56.2)	0.848

ASA=American Society of Anesthesiologists; ENT=ear, nose, and throat; GFR=glomerular filtration rate; IQR=interquartile range; MAC=minimal alveolar concentration; NSAIDs=non-steroidal anti-inflammatory drugs; PRC=pack red cell; SD=standard deviation

* Statistical significance

Table 5. Multivariable analysis of independent factors associated with postoperative acute kidney injury

	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
ASA classification (Ref.: class 1)			
Class 2	8.17 (1.1 to 61.3)	7.82 (1.0 to 59.2)	0.046
≥ Class 3	10.5 (1.4 to 80.6)	9.85 (1.3 to 76.4)	0.029
Body mass index (Ref.: normal)			
Underweight	0.42 (0.1 to 1.2)	0.42 (0.1 to 1.2)	0.128
Overweight	0.68 (0.4 to 1.3)	0.63 (0.3 to 1.2)	0.160
Obese	6.54 (2.3 to 18.6)	5.74 (2.0 to 16.4)	0.001
Sevoflurane exposure (Ref.: ≤2 MAC-hour)	0.9 (0.6 to 1.5)	0.89 (0.5 to 1.5)	0.666

ASA=American Society of Anesthesiologists; CI=confidence interval; Ref.=reference; MAC=minimal alveolar concentration; OR=odds ratio

patients receiving low-flow sevoflurane was 20.8%. Administration of sevoflurane exceeding two MAC-hours did not predispose clinical postoperative renal injury with an adjusted odds ratio of 0.89 (95% CI 0.5 to 1.5, p=0.666). Thus, it may have a protective effect for the immediate postoperative AKI incidence, which was significantly lower than another group (p=0.015).

What is already known on this topic?

Prolonged sevoflurane exposure increases nephrotoxic metabolites, such as serum fluoride and compound A. Medium to high flow sevoflurane did not result in clinical renal injuries. Previous studies implemented sCr and GFR criteria of the KDIGO's criteria to diagnose postoperative AKI.

What this study adds?

Prolonged use of sevoflurane in low-flow anesthesia exceeding two MAC-hour does not increase the risk of postoperative AKI. On the contrary, the incidence of immediate postoperative AKI was lower than the patients receiving less than two MAC-hours group. Mostly, kidney injuries developed within 24 hours postoperatively.

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Conflicts of interest

The authors declare no conflict of interest.

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