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Research Article

Comparison the Cerebroprotective Effect of Sevoflurane and Propofol in Patients with Carotid Artery Stenosis Undergoing Coronary Artery Bypass Grafting: A Randomized Clinical Study

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Abstract

Objective: The Objective of the study was to evaluate the perioperative cerebral protective effect of sevoflurane and propofol in patients with carotid artery stenosis undergoing coronary artery bypass grafting. Materials and Methods: A randomized clinical study included 200 patients with preoperative carotid artery stenosis <50% scheduled for cardiac surgery with cardiopulmonary bypass. The patients were classified into 2 groups (each=100), Sevoflurane group: The patients received sevoflurane (concentration 1% to 4%) as an inhalational agent. Propofol group: The patients received propofol infusion (4-6 mg/kg/hr). The sevoflurane and propofol were given during the whole procedure (before, during, and after cardiopulmonary bypass). The monitors included heart rate, mean arterial blood pressure (MAP), central venous pressure and cerebral near-infrared spectroscopy (NIRS), the incidence of postoperative cognitive dysfunction and stroke. Results: There was no significant difference in the perioperative heart rate, mean arterial blood pressure, central venous pressure, and the right or left regional cerebral oxygen saturation between the two groups (P>0.05). The incidence of postoperative neurological complication was significantly lower with sevoflurane than propofol (P=0.012). The incidence of delirium was significantly lower with sevoflurane than propofol (P=0.023). The incidence of stroke was lower with sevoflurane than propofol, but the difference was insignificant (P=0.682). The ICU and hospital length of stay were shorter with sevoflurane than propofol (P=0.013, P=0.033 respectively). Conclusions: The sevoflurane was associated with a lower incidence of postoperative cognitive dysfunction than propofol in patients with carotid artery stenosis undergoing coronary artery bypass grafting.

Keywords

Carotid Artery Stenosis, Sevoflurane, Propofol, Coronary Artery Bypasses Grafting, Delirium, Stroke

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1. Introduction

Brain tissue is extremely sensitive to ischemia and prone to injuries such as stroke and neurocognitive dysfunction after cardiac surgery with cardiopulmonary bypass (CPB). These complications may be related to cerebral embolisms and hypoxia. [1, 2] The incidence of postoperative neurological complications (stroke and neurocognitive dysfunction) ranges from 6-41% after cardiac surgery. [3]

The incidence of carotid artery disease in patients undergoing coronary artery bypass grafting (CABG) varies from 2% to 22%. [4, 5] The presence of carotid artery stenosis may result in cerebral hypoperfusion and therefore, it is a risk factor for the development of neurologic injury following cardiac operations. [6]

Sevoflurane and propofol are the most two common anesthetic agents in clinical practice [7] and used for cerebral protection to decrease the incidence of cognitive dysfunction during cardiac surgery. [8]

We hypothesized that sevoflurane and propofol provide an equal cerebral protection in patients with carotid artery stenosis undergoing coronary artery surgery.

The aim of the present study was to evaluate the perioperative cerebroprotective effect of sevoflurane and propofol in patients with carotid artery stenosis undergoing coronary artery bypass grafting.

2. Materials and Methods

After obtaining informed consent and approval of local ethics and research committee in the cardiac center (82/2018, 25/08/2018), a prospective randomized study included 200 patients undergoing coronary artery bypass grafting using cardiopulmonary bypass (November 2018-May 2023). The inclusion criteria were patients with preoperative carotid artery stenosis <50% (unilateral or bilateral), hypertension, diabetes, ejection fraction ≥45%. Exclusion criteria included patients with valvular surgery, previous neurologic diseases, congestive heart failure, acute myocardial infarction, emergency, atrial fibrillation or obstructive cardiomyopathy, off-pump coronary artery bypass grafting (CABG), renal or hepatic impairment. The patients were randomly allocated (the concealment of allocation was done by using random numbers generated through excel) into two equal groups (n=100 each). Sevoflurane group: The patients received sevoflurane (concentration 1% to 4%) as an inhalational agent during the whole procedure (before, during, and after cardiopulmonary bypass) and the concentrations of sevoflurane were recorded every 5 minutes during the procedure using Dräger, Fabius GS, Premium Germany. Propofol group: The patients received propofol infusion (4-6 mg/kg/hr) during the whole procedure (before, during, and after cardiopulmonary bypass).

The patients with postoperative neurological complications were assessed by neuropsychiatrist on the 2nd, 4th, and 6th postoperative days for the diagnosis of neurocognitive dysfunction or stroke.

For all patients and under local anesthesia, a radial arterial cannula and central venous line were inserted guided by ultrasound before the operation to enable continuous hemodynamic monitoring. Induction was done by intravenous fentanyl (3-5µg/kg), etomidate (0.3mg/kg), rocuronium (0.8mg/kg). The anesthesia was maintained with oxygen/air (50%), fentanyl infusion (1-3µg/kg/hr), cisatracurium (1-2µg/kg/min), and sevoflurane or propofol according to the study medication protocol. At the end of surgical intervention, the patients were prepared for weaning from CBP. If there was difficulty to wean from CPB, pharmacological support (dopamine or epinephrine or norepinephrine, or nitroglycerine), mechanical support (IABP) or pacing were started. At the end of surgery, the patients were transferred to the cardiac surgery ICU with full monitoring.

Cardiopulmonary bypass was established with cannulation of the ascending aorta and right atrium. The patients received cold blood cardioplegia in the standard ratio (4:1) four parts of blood from the cardiopulmonary bypass circuit, and one part potassium-rich crystalloid named Plegisol (Hospira, Inc, Lake Forest, IL, USA). The initial dose was 30 ml/kg, and subsequent doses were 20 ml/kg given every 20 min. The temperature was reduced to 28°C while maintaining a perfusion pressure of 100-125 mmHg. In the two groups, cardioplegia solution was given two-thirds through the antegrade and one-third through the retrograde route, and a hot shot (warm blood) antegrade dose was given just before the myocardium reperfusion.

Hemodynamic monitoring included the heart rate; mean arterial blood pressure (MAP), a continuous electrocardiograph with automatic ST-segment analysis (leads II and V), central venous pressure, and cerebral near-infrared spectroscopy (NIRS) to measure the regional cerebral oxygen saturation. The patients with postoperative neurological complications were assessed by neuropsychiatrist before surgery, the 2nd, 4th, and 6th postoperative days for the diagnosis of neurocognitive dysfunction or stroke. Postoperatively, the CT scan or MRI brain was done in patients with neurological complications.

Hemodynamic values were serially collected at the following timepoints: T0: Baseline reading; T1:15 minute after induction; T2: before cardiopulmonary bypass; T3: 30 minutes after cardiopulmonary bypass; T4: at ICU admission; T5: 6th hour after ICU admission; T6: 12th hour after ICU admission; T7: 24th hour after ICU admission. In addition to the previous timepoints, regional cerebral oxygen saturation was assessed during CPB at the 15th, 30th minute after initiation of CPB and five minutes before weaning of CPB. The neurological functions were evaluated before surgery, the 2nd, 4th, and 6th postoperative.

The primary outcome was the cerebral protective effect

diagnosed by the incidence of the acute brain injury (stroke), and delirium symptoms (neurocognitive dysfunction such as the inability to concentrate, amnesia, confusion, anxiety, the feeling of imbalance, changes in vision, and abnormal behavior of the patients). Secondary outcomes were the requirement for pharmacological and mechanical support in addition to the safety of the study medications, which was assessed by the occurrence of any adverse events.

Power analysis was performed using the Chi square test for independent samples on the frequency of patients associated with neurological complications because it was the main outcome variable in the present study. A pilot study (20 patients in each group) was done before starting this study because there is no available data in the literature for the comparison of the cerebral protective effect of sevoflurane and propofol in patients with carotid artery stenosis undergoing coronary artery surgery. The results of the pilot study showed that the incidence of postoperative neurological complication was 10% in sevoflurane group, and 25% in propofol group. Taking power 0.8, alpha error 0.05, and beta 0.2, a minimum sample size of 100 patients was calculated for each group.

Statistical Methods: Data were statistically described in terms of mean ± standard deviation (± SD), or frequencies (number of cases) and percentages when appropriate. A comparison of numerical variables between the study groups was done using the Student t-test for independent samples. Repeated measure ANOVA was used to see the effect of sevoflurane and propofol on hemodynamics and regional cerebral oxygen saturation at different follow-up intervals. For comparing categorical data, Chi-square (X^2) test was performed. Exact test was used instead when the expected frequency is less than 5. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

3. Results

Table 1 shows no significant differences regarding the demographic data, co-morbidities, preoperative medications, NYHA class, Euroscore, and the ASA physical status score (P>0.05).

Table 2 shows the changes in the hemodynamics of patients during the procedure and through the first 24 hours in the ICU. There was no significant difference in the perioperative heart rate, mean arterial blood pressure and central venous pressure between the patients of the two groups (P>0.05).

Table 3 shows the changes in the regional cerebral oxygen saturation. There was no significant difference in the right or left regional cerebral oxygen saturation as measured by cerebral near-infrared spectroscopy before, during or after the CPB between the two groups (P>0.05).

Table 4 shows the intraoperative data and the outcomes of patients of the two groups. There was no difference in the number of coronary artery grafts, cardiopulmonary bypass time, cross clamping time, blood loss, transfused packed red blood cells, intraoperative fluid, hematocrit value, urine output, blood sugar and postoperative renal complications between the two groups (P>0.05). The weaning from CPB was easier in patients of the sevoflurane group than the propofol group. Patients of the sevoflurane group needed smaller doses of pharmacological support (dopamine, epinephrine, norepinephrine, and nitroglycerine) than the propofol group (P<0.05), and the requirement for mechanical support (IABP) and the pacing was lower in patients of the sevoflurane group than the propofol group (P<0.05). The total number of patients who suffered from postoperative neurological complications was significantly lower in patients of the sevoflurane group compared to the propofol group (P=0.012). The incidence of delirium (neurocognitive dysfunction) was significantly lower in the sevoflurane group than the propofol group (P=0.023). The incidence of stroke was lower in the patients of sevoflurane group compared to the propofol group, but the difference was insignificant (P=0.682). The ICU and hospital length of stay were shorter in the sevoflurane group than the propofol group (P=0.013, P=0.033 respectively). The incidence of mortality was lower in the sevoflurane group than the propofol group, but the difference was insignificant (P=0.213).

Table 1. *Preoperative data of patients (Data are presented as mean±SD, Number, %).*

Variable	Sevoflurane group (n=100)	Propofol group (n=100)	P-value
Age (year)	57.38±13.12	56.85±12.62	0.771
Weight (Kg)	85.40±12.55	86.30±12.10	0.606
Gender Male: Female	76:24	68:32	0.270
Diabetes mellitus	85	89	0.528
Hypertension	86	80	0.346
Ischemic heart disease	100	100	1.000

Variable		Sevoflurane group (n=100)	Propofol group (n=100)	P-value
Atrial fibrillation		31	27	0.640
Pulmonary hypertension		24	29	0.521
Ejection fraction (%)		50.55±5.78	51.40±6.10	0.313
Angiotensin-converting-enzyme inhibitors		80	86	0.346
Beta-blockers		83	79	0.589
Calcium channels-blockers		30	39	0.233
Aspirin		100	100	1.000
Statins		89	93	0.459
	<50%	100	100	1.000
Carotid stenosis	Unilateral	31	36	0.549
	Bilateral	69	64	0.549
Smoking		64	55	0.249
	II	26	35	0.219
NYHA	III	65	58	0.383
	IV	9	7	0.795
	III	83	88	0.422
ASA	IV	17	12	0.422
Euroscore (%)		13.15±3.85	12.74±3.17	0.412
Body surface area (m²)		1.78±0.15	1.76±0.18	0.394
Coronary artery bypasses grafting		100	100	1.000

NYHA: New York Heart Association; ASA: American Society of Anesthesiologists Physical Status Score.

Table 2. *Heart rate, mean arterial blood pressure and central venous pressure of patients (Data are presented as mean±SD).*

Variable		Sevoflurane group (n=100)	Propofol group (n=100)	P-value
Heart rate (bpm)	T0	76.45±11.70	77.36±10.42	0.562
	T1	74.22±9.80	75.50±9.00	0.337
	T2	72.27±7.49	73.07±8.16	0.471
	T3	74.20±8.10	74.85±9.15	0.595
	T4	78.90±9.30	79.18±10.38	0.841
	T5	80.27±11.29	79.40±12.80	0.610
	T6	81.20±12.74	82.10±13.30	0.625
	T7	80.90±11.00	81.35±12.21	0.784
Mean arterial blood pressure (mmHg)	T0	107.90±14.25	104.46±13.70	0.083
	T1	103.80±13.55	105.40±14.83	0.426
	T2	105.65±13.77	103.19±15.10	0.230
	T3	104.22±12.60	106.30±13.60	0.263

Variable		Sevoflurane group (n=100)	Propofol group (n=100)	P-value
Central venous pressure (mmHg)	T4	109.93±15.80	112.10±14.05	0.306
	T5	112.64±14.00	114.14±16.40	0.487
	T6	114.60±15.30	115.73±16.20	0.612
	T7	110.20±11.32	112.38±14.45	0.236
	T0	10.15±1.24	10.43±1.45	0.143
	T1	11.47±1.85	11.82±1.90	0.188
	T2	12.42±1.38	12.63±1.60	0.321
	T3	12.59±1.90	12.36±1.63	0.359
	T4	13.14±1.27	12.79±1.65	0.094
	T5	12.47±2.00	13.00±1.89	0.055
	T6	12.75±1.55	12.90±1.81	0.529
	T7	12.54±1.37	12.17±1.48	0.068

T0: Baseline reading; T1:15 minute after induction; T2: before cardiopulmonary bypass; T3: 30 minute after cardiopulmonary bypass; T4: at ICU admission; T5: 6th hour after ICU admission; T6: 12th hour after ICU admission; T7: 24th hour after ICU admission.

Table 3. *Regional cerebral oxygen saturation of patients (Data are presented as %).*

Variable			Sevoflurane group (n=100)	Propofol group (n=100)	P-value
Right regional cerebral oxygen saturation (%)	T0		69.30±3.21	68.90±2.85	0.352
	T1		72.30±2.26	71.83±2.50	0.164
	T2		72.29±1.97	72.08±2.15	0.472
	CPB	15 min	63.36±4.62	64.41±4.99	0.124
		30 min	65.60±5.37	64.90±4.87	0.335
		5 min before weaning	65.08±4.70	63.95±4.26	0.076
	T3		70.60±3.12	71.20±2.39	0.128
	T4		72.00±2.35	71.57±2.20	0.183
	T5		71.35±3.46	71.68±4.10	0.539
	T6		69.60±2.15	70.24±3.00	0.084
	T7		70.44±3.40	70.20±3.17	0.606
Left regional cerebral oxygen saturation (%)	T0		70.64±2.07	70.17±1.96	0.100
	T1		71.47±3.30	71.20±2.93	0.541
	T2		72.38±3.55	71.90±3.24	0.319
	CPB	15 min	65.34±2.30	64.79±2.17	0.083
		30 min	64.70±2.13	64.35±2.26	0.261
		5 min before weaning	66.20±2.80	65.92±3.18	0.509
	T3		73.53±3.85	72.78±3.40	0.145
	T4		72.38±2.90	71.75±2.47	0.099

Variable	Sevoflurane group (n=100)	Propofol group (n=100)	P-value
T5	73.25±2.73	72.83±2.80	0.284
T6	71.76±2.15	72.25±2.40	0.129
T7	72.33±2.30	72.56±2.50	0.499

T0: Baseline reading; T1: Reading 15 minutes after induction; T2: before initiation cardiopulmonary bypass; CPB 15 min: 15 minutes after initiation of cardiopulmonary bypass; CPB 30 min: 30 minutes after initiation of cardiopulmonary bypass; CPB 5 min: five minutes before weaning of cardiopulmonary bypass; T3: 30 minutes after cardiopulmonary bypass T5: 30 minutes after cardiopulmonary bypass; T6: at ICU admission; T9: 6th hour after ICU admission; T10: 12th hour after ICU admission; T7: 24th hour after ICU admission.

Table 4. *Intraoperative data and outcome of patients (Data are presented as mean±SD, Number, %).*

Variable		Sevoflurane group (n=100)	Propofol group (n=100)	P-value
Number of coronary artery grafts	2	14	18	0.563
	3	22	28	0.414
	4	55	49	0.479
	5	6	3	0.495
	6	3	2	0.650
CPB time (minute)		114.45±22.50	109.90±20.28	0.134
Cross clamping time (minute)		90.57±15.20	87.42±12.44	0.110
Dopamine (μg/kg/min)		7.15±3.70	8.46±3.98	0.016*
Epinephrine (μg/kg/min)		0.06±0.02	0.07±0.03	0.006*
Norepinephrine (μg/kg/min)		0.04±0.02	0.05±0.03	0.006*
Nitroglycerine (μg/kg/min)		0.6±0.30	0.7±0.32	0.023*
Intra-aortic balloon pump		24	39	0.032*
Pacing		21	35	0.040*
Transfused P-RBC (unit)		3.66±0. 81	3.49±0.63	0.099
Hematocrit (%)		37.26±3.15	36.98±3.00	0.520
Blood loss (ml)	Intraoperative (ml)	2150.63±248.37	2210.52±254.70	0.093
	Postoperative (ml/24 hr)	590.85±140.48	625.62±155.70	0.098
Intraoperative fluids	Crystalloids (ml)	3124.70±574.20	3213.80± 614.00	0.290
	Hesteril 6 % (ml)	590.85±1 21.46	610.97±1 35.74	0.270
Intraoperative urine output (ml)		2080.75±195.84	2122.10±227.40	0.169
Intraoperative blood sugar levels (mmol/L)		8.01±1.20	8.15±1.31	0.431
Postoperative neurological complications	Total	16	32	0.012*
	Delirium	8	19	0.037*
	Amnesia	6	9	0.592
	Stroke	2	4	0.682
Postoperative renal impairment		8	6	0.782
Postoperative renal failure		4	2	0.682

Variable		Sevoflurane group (n=100)	Propofol group (n=100)	P-value
Postoperative dialysis	Temporarily	2	1	0.560
	Permanent	1	1	1.000
ICU length of stay (days)		3.75±1.20	4.24±1.55	0.013*
Hospital length of stay (days)		7.90±2.71	8.80±3.20	0.033*
Mortality		3	8	0.213

*P<0.05 significant comparison between the two groups.
CPB: Cardiopulmonary bypass; P-RBC: Packed- red blood cells; ICU: Intensive care unit.

4. Discussion

The present studies showed that the cerebral protective effect and neurological outcome with sevoflurane were better more than the propofol in patients with carotid artery stenosis undergoing coronary artery surgery. The incidence of delirium symptoms (neurocognitive dysfunction such as the inability to concentrate, amnesia, confusion, anxiety, the feeling of imbalance, changes in vision, and abnormal behavior of the patients) was lower with sevoflurane than propofol but there was no difference in the incidence of the stroke. There was no difference in the values of regional cerebral oxygenation as measured by cerebral near-infrared spectroscopy (NIRS). There was no relation between the neurological outcome and the NIRS.

There are many studies that support the findings in the present study and showed that inhalation anesthesia is superior to total intravenous anesthesia in terms of their cerebroprotective effect during cardiac surgery using CPB. [9-15]

Schoen et al. [8] showed that patients with impaired preoperative cognitive performance have a better short-term postoperative cognitive performance with sevoflurane than propofol.

Zhu et al. [15] showed that both sevoflurane and propofol maintain the balance of cerebral oxygen metabolism in patients undergoing cardiac surgery under CPB, but the sevoflurane provides an ideal protective effect on postoperative neurological function.

Güçlü et al. [11] found that cerebral oxygen saturation was higher in the sevoflurane group than in the TIVA group and the effect of sevoflurane were useful for maintaining the cerebral oxygen saturation during CBP.

In patients aged 65 to 86 years undergoing tumor resection, sevoflurane did not increase the incidence of postoperative cognitive dysfunction compared to propofol at 7 days or 3 months after surgery or impact short-term postoperative prognosis. [16]

A meta-analysis study showed that cerebral protection and neurological outcome were significantly better with the inhalational agents than those of the total intravenous agents (TIVA) for patients undergoing cardiac surgery with CPB. The analysis showed no significant difference in the arteriovenous oxygen content difference, cerebral oxygen extraction ratio, and jugular bulb venous oxygen saturation between the two groups. This analysis did not focus on patients with carotid artery stenosis. [13] Also, another study showed that the improvement of neurological function with sevoflurane and it can reduce the incidence of postoperative cognitive dysfunction in elderly patients undergoing cardiac surgery. [17]

Although there was no significant difference in the regional cerebral oxygenation between the sevoflurane and propofol, the postoperative cognitive function was better with sevoflurane than the propofol and this supported by the study that showed inhalational anesthesia and total intravenous anesthesia can provide adequate cerebral oxygen supply without significant fluctuations during CPB. [11]

El-Morsya et al. [18] showed that sevoflurane provides a wider range of safety against impaired cerebral oxygenation and better stability of systemic hemodynamics compared to the propofol. Also, the study reported that cerebral oxygen saturation may not reflect changes in cerebral oxygenation as monitored by jugular venous oxygen tension measurement in children undergoing CPB. Doe et al. [19] showed that sevoflurane maintains higher jugular venous bulb oxygenation levels than propofol during steep Trendelenburg position and pneumoperitoneum for robotic-assisted laparoscopic prostatectomy. Also, the regional oxygen saturation does not reflect jugular venous bulb oxygenation. In a systemic review, Serraino et al. [20] showed that cerebral NIRS monitoring did not have clinical benefits in cardiac surgery.

Excessive secretion and aggregation of excitatory amino acids within the brain tissue during CPB is associated with the occurrence of postoperative neurological dysfunction. The excitatory amino acids within the brain tissue lead to continuous activation of postsynaptic membrane and increase the permeability damage of neurons, resulting in postoperative cognitive dysfunction. [15, 21] The sevoflurane inhibits the synthesis of excitatory amino acids during CPB, and it could decrease the postoperative cognitive dysfunction. [22] Sevoflurane has a direct cerebral vasodilatory effect, increases cerebral blood flow, and plays a role in brain protection by reducing cerebral metabolic rate. [21]

The sevoflurane maintains cerebral hemodynamics as reported by a study that showed propofol decreases the maximum cerebral blood flow velocity, mean cerebral blood flow velocity, and mean arterial blood flow more than sevoflurane. [23] Experimental studies show that cerebroprotective effect of inhalation anesthetic agents may be related to the preconditioning [24] which attenuate apoptosis and necrosis of cerebral neurons, thereby reducing neurological dysfunction after ischemia. Also, the inhalation agents provide the stability of hemodynamics and therefore maintain the adequate perfusion and oxygenation of the organs, [25] and improve the recovery and survival of patients after surgery. Previous studies showed that propofol causes a global decrease in regional cerebral blood flow more than the sevoflurane. [23, 26]

In spite of the association between intraoperative cerebral oxygen desaturation and postoperative cognitive dysfunction, stroke, and prolonged hospital stay, [27-29] there was no any desaturation in patients with a postoperative neurological complication in the present study as measured by NIRS and the regional cerebral oxygenation was maintained as the preoperative, intraoperative and postoperative range. There are limitations to the present study. First, the study was not a blinded study, and second, it was done in a single center.

5. Conclusion

The sevoflurane induces a better cerebroprotective effect than propofol. It decreases the incidence of postoperative cognitive dysfunction more than the propofol in patients with carotid artery stenosis undergoing coronary artery bypass grafting.

Abbreviations

CPB: Cardiopulmonary Bypass
CABG: Coronary Artery Bypass Grafting
MAP: Mean Arterial Blood Pressure
NYHA: New York Heart Association
ASA: American Society of Anesthesiologists Physical Status Score
IABP: Intra-Aortic Balloon Counterpulsation
TIVA: Total Intravenous Agents
NIRS: Cerebral Near-Infrared Spectroscopy
P-RBC: Packed- Red Blood Cells
ICU: Intensive Care Unit

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Author Contributions

Rabie Nasr: They were responsible for anesthesia of the cases, collection the data of patients, analysis of results and the writing of discussion.

Ahmed Soliman: He was responsible for analysis of results and the writing of discussion

Conflicts of Interest

The authors declare no conflicts of interest.

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