Int J Clin Exp Pathol 2017;10(2):2053-2061
www.ijcep.com /ISSN:1936-2625/IJCEP0039373

Original Article

Sufentanil attenuates cardiopulmonary bypass-associated brain injury in a rat model

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Received August 4, 2016; Accepted November 8, 2016; Epub February 1, 2017; Published February 15, 2017

Abstract: In cardiac surgery, the occurrence of brian injury is usually associated with cardiopulmonary bypass (CPB). To address this issue, here we studied the neuroprotective role of sufentanil in alleviating of CPB-associated brain injury in a rat model. The rats used in the experiment were divided into 4 groups: (1) sham-operated group (no CPB); (2) rats subjected to vehicle pretreatment (placebo group); (3) & (4) rats received sufentanil 1 (S1 group) or 5 (S5 group) μg/kg body weight before the onset of CPB. Sufentanil infusion was maintained at 90 (S1 group) or 300 (S5 group) μg/kg body weight/min during CPB 60 min after the surgery. The rat brain was collected and dissected for measuring cerebral water content (CWC) and calcium concentration for the evaluation of cerebral edema and intracellular calcium accumulation. The levels of S-100β in plasma were assessed as a biomarker for cerebral neuronal death. Rat from the placebo group has a much higher levels of CWC and calcium as compared to those from sham-operated group. However, Sufentanil infusion (i.e. Rat from S1 and S5 group) can dramatically decrease CWC level. Similar results were also observed in S-100β level in plasma. Our study indicates that the decrease of CPB-induced cerebral edema, intracellular calcium overload, as well as neuronal death are associated with the neuroprotective effect of sufentanil.

Keywords: Sufentanil, cardiopulmonary bypass, brain injury, neuroprotective effect

Introduction

In cardiac surgery such as frank stroke and hypoxic encephalopathy, brain injury is associated with the cardiopulmonary bypass (CPB) [1, 2]. Although the etiology of CPB-induced brain injury is not thoroughly understood, several factors potentially contribute to the compromise of brain functional integrity, including genetic susceptibility (*e.g* apolipoprotein genotype), cerebral edema, neuronal cell death, systemic inflammatory responses, cerebral microemboli induced by atherosclerotic debris, air bubble, and fat deposit, impaired cerebral perfusion and oxygenation [1-3]. Rat CPB was originally developed to study the mechanism of postoperative cognitive dysfunction (POCD) associated with CPB; recently, it has been widely utilized to explore the mechanisms associated with neurologic and neurocognitive impairment during CPB procedure [4, 5]. Additionally, this model has also been employed to develop neuroprotective strategies to address the adverse effects in the central nervous system (CNS) associated with CPB [6-8].

S-100β protein is usually used as a biochemical marker for central nervous system injury, such as traumatic brain injury, subarachnoid haemorrhage and stroke [9]. Interestingly, glial and Schwann cells in the brain usually over-expresses S100 proteins [10, 11]. Disruption of neuronal cell membrane integrity in the brain can lead to the leakage of intracellular S-100β protein into the plasma [12, 13]. In addition, dysfunctional blood-brain barrier can also increase S-100β protein levels in the serum. Therefore, S-100β level in plasma are now connected with

brain injury, such as traumatic brain injury, subarachnoid haemorrhage, hypoxic ischemic encephalopathy (HIE) and stroke [14]. Sufentanil is a powerful synthetic opioid analgesic drug-around 5 to 10 times more potent than its analog, fentanyl; 400 to 1000 times more powerful than morphine [15]. It is usually administered when pain relief is required for a short period of time. Additionally, it also offers properties of sedation since it is an analgesic component of anaesthetic regimen.

In this study, we investigated the impact of sufentanil in ameliorating of cerebral injuries induced by CPB. Cerebral water content (CWC) was measured to show whether sufentanil treatment would alleviate cerebral edema. To evaluate the effect of sufentanil treatment on the cerebral calcium accumulation, we also examined the total calcium concentration. The impairment of cerebral calcium ion homeostasis can yield neuronal degeneration and cell death after cerebral ischema, fluid-percussion brain trauma, or cortical contusion in rats [11, 16]. Addtionally, S-100β protein levels in the serum were measured to test the neuroprotective role of sufentanil in cerebral malfunction induced by neuronal cell death.

Materials and methods

Animals

The animal work described in this study was approved with the Protocols for Animal Use (IACUC protocol number: 08192012015YUIACUC, approved on Aug. 19, 2012) by the Medical School of Yangtze University's Institutional Animal Care and Use Committee (IACUC). Sprague-Dawley (SD) adult male rats (body weight: 400±20 g) were obtained from Animal center at Yangtze University. The rats were randomly divided into 4 groups: (1) Sham rats that were cannulated but did not undergo CPB (CPB sham group); (2) Rats exposed to vehicle pretreatment followed by CPB (placebo group); (3) Rats received sufentanil preadministration (1 μg/kg body weight) before CPB (S1 group). Sufentanil infusion was maintained at 90 μg/kg body weight/min during CPB. This condition was maintained in 60 min during recovery after the surgery; and (4) Rats administered with sufentanil prior to CPB (5 μg/kg body, i.v. injection) (S5 group). Sufentanil administration was maintained by intravenous infusion during the surgery as well as in the postoperative recovery by means of an infusion pump (Braun, Melsungen) at 300 μg/kg body weight/min for the animals in this group. No accidental deaths occurred. Rat euthanasia were performed with CO_2. Briefly, the rats were gradually exposed to CO_2 for around 12-20 mins, followed by decapitation to ensure the euthanasia was successful.

Surgical preparation and cardiopulmonary bypass (CPB)

Animals were anesthetized with halothane prior to the surgery. Briefly, halothane was administered at a concentration up to 1% in oxygen. The maintenance of anaesthesia were achieved by the following methods: inhalation of 0.3% halothane in air was first performed, followed by using halothane at a concentration of 1-3% in a mixure of nitrous oxide/oxygen (oxide/oxygen ratio: 70/30 or 50/50). In our operation regimes, the breathing was spontaneous. The artificial ventilation through a tracheal cannula was not employed unless the spontaneous ventilation was successful.

The trachea was subsequently intubated and ventilation was adjusted to maintain an arterial carbon dioxide tension ($PaCO_2$) of 36-42 mmHg. Vecuronium Bromide (0.1 mg/kg body weight) was intraperitoneally administered. Mean arterial blood pressure was monitored continuously via right femoral artery, which was cannulated with a 22-G heparinized intravenous catheter. 500 IU/kg heparin was delivered intravenously before the onset of CPB. The recoverable rat CPB model in the current study was modified from a previously reported version [4]. Briefly, the tail artery was dissected and cannulated with a 14-G intravenous catheter, which served as the arterial inflow for the CPB circuit. Through a horizontal neck incision, the right internal jugular vein was cannulated with a 14-G catheter that was modified to include a 4.5 F, dual-stage venous cannula. This multiorificed venous cannula was inserted and further advanced until the cannula tip reached the junction of the inferior vena cava and right atrium. The catheter located at the right jugular vein was used for venous return to the CPB circuit. As a venous reservoir to collect blood from the venous return tubing in the CPB circuit, a 5-mL cylinder syringe was positioned 40 cm below the heart level to create gravity-gradient

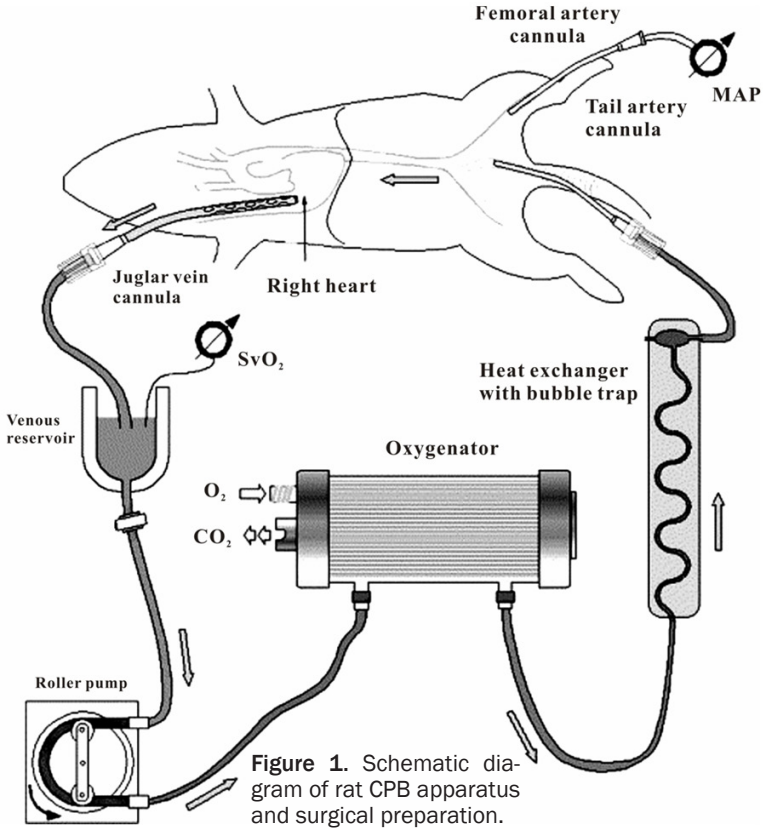

Figure 1. Schematic diagram of rat CPB apparatus and surgical preparation.

drainage of the inferior vena cava, superior vena cava, and coronary sinus. As shown in **Figure 1**, the CPB circuit consisted a venous reservoir, a peristaltic pump (Mosterflex digital standard drive pump, Cole-Parmer Instrument Co., USA), a miniaturized membrane oxygenator (with a surface area of 0.09 m^2, Shanghai Fudan Biomaterials, LLC., China), and the arterial inflow cannula. All the components of the CPB circuit were connected via silicone tubing (1.6 mm ID). The oxygenator contains a heating/cooling chamber to achieve an effective maintenance of a constant body temperature within a narrow, predetermined range. The venous blood returning through the venous cannula to the venous reservoir was drained to the peristaltic pump. When pumped through the membrane oxygenator, the oxygenated blood was directed into the tail arterial inflow catheter.

The CPB circuit was primed with approximately 20 ml of the circuit prime solution, which was composed of 12 ml lactated Ringer's solution, 7 ml of 6% hydroxyethyl starch solution, and 1 ml of Mannitol. During CPB, crystalloid solutions were added to the circuit at a ratio of 1:1 to maintain a constant blood level of 2-3 ml in the venous reservoir. At the beginning of CPB, the circuit flow was initiated at ~100 mL/kg body weight/min and eventually increased to ~160 mL/kg body weight/min, similar to the normal cardiac output in the rat. The flow rate was maintained at this level for the rest of the process. Dissolved oxygen levels were maintained at 0.2~0.5 L/min and were monitored continuously at the caudal epigastric artery cannulated with an intravenous catheter during the surgery. The rectal temperature was monitored and maintained at 28-30°C during CPB. 20 min before the next operation, the rats were relieved from CPB by a stepwise decrease in the flow rate. The rats were then disconnected from the circuit. Rectal temperature was restored to 36-37°C. The entire CPB process lasted ~1.5 hours.

During CPB, anesthesia was maintained in the presence of 2% halothane. After CPB was terminated, the animals were allowed to recover for ~1 hour before sacrifice. Rat brain was dissected out and the amount of water content and total calcium was measured. The level of S-100β in the serum were examined with ELISA. Management of rats under neuromuscular blockade was performed as follows: After neuromuscular blockade, the four arms of rats were connected and monitored by a multiparameter monitor to monitor the electrocardiogram ECG of rats. Rat body temperature was monitored via measuring the rectal temperature at 2 cm insides the rectum. Femoral artery puncture is performed with 24 G needles. A pressure converter was connected to the monitor to observe the blood pressure. Hear rate was monitored during the whole cardiopulmonary bypass (CPB) process. Rats blood pH was monitored and controlled at pH = 7.35~7.45, $PaCO_2$ = 35~45 mmHg and BE = -3~3 mmol/L.

Table 1. Hemodynamics

Index	Group	Pre-CPB	CPB 30 min	CPB 60 min	CPB 90 min	Post-CPB 30 min	Post-CPB 60 min
MAP (mmHg)	Sham-operated	95.3±12.1	96.9±10.8	100.5±12.2	103.4±12.6	97.8±9.0	98.0±10.9
	Placebo	99.7±15.2	69.8±11.4**	70.1±9.1**	71.9±6.6**	88.5±8.4*	91.3±9.9
	S1	101.4±12.7	73.3±8.8**	72.6±7.6**	73.0±7.9**	89.4±8.5*	94.1±11.1
	S5	97.6±12.5	72.2±9.4**	71.8±8.5**	70.7±7.4**	90.2±7.6*	95.21±10.5
HR (bpm)	Sham-operated	249.8±41.9	236.1±44.1	230±47.2	231.3±43.3	233.8±46.8	228.1±45.5
	Placebo	237.1±34.2	211.9±39.4	198.6±38.6	201.4±43.8*	209.8±37.2	212.0±33.6
	S1	238.5±46.8	189.3±36.7*	185.3±41.4*	195.3±44.2*	194.9±39.2*	202.0±33.6
	S5	233.7±44.1	182.6±44.7*	176.1±42.8*	187.1±47.5*	186.5±35.6*	199.5±42.3

Mean arterial pressure (MAP), heart rate (HR) (n = 6, CPB & non-CPB) 5 min before CPB, 30, 60, 90 min after the onset of CPB, and 30, 60 min after CPB disengagement. Compared to the sham-operated group, *P < 0.05; **P < 0.01.

Cerebral water content (CWC) and total calcium measurements

After one-hour post-operative stabilization period upon CPB disengagement, the skull was opened and the brain was removed immediately afterwards. The right and left hemispheres were divided from each other, and the right hemisphere was harvested for measuring the amount of water. Excess fluid (water and blood) was removed by absorbent paper towels before the right hemisphere was weighed. After being dried in an oven at 60°C for 72 hours, the right hemisphere was reweighed on the same scale. The difference between the initial and final weights was assumed to be the weight of the total water content in the right hemisphere. The total water content in the right hemisphere (%) was calculated as: (wet weight-dry weight)/wet weight × 100. The left hemisphere was used for measuring the amount calcium. After the tissues were weighed, a 4:1 mixture of concentrated HNO_3: $HClO_4$ acids was added for overnight. After removal of acids by means of temperature gradient (ranging from 60 to 120°C), the samples were then diluted in ultra-pure water and read in an inductively coupled plasma optical emission spectrometer (ICPAES). The analytical line used was 393.366 nm for calcium (LOD = 0.0001 mg/L, radial view).

ELISA

1 hour after CPB disengagement, 3 ml of venous blood was collected from each animal. After being incubated at room temperature for 20 minutes, the blood samples were centrifuged at 4,000 r/min for 10 minutes. The yellow plasma layer was then transferred to another tube. S-100β protein level was measured quantitatively with an ELISA kit (S100beta Protein ELISA Kit (Rat), GBD, U.S.A).

Statistical analysis

The statistical analysis was performed with SPSS 11.5 software (SPSS Inc, Chicago, IL). Data are expressed as the mean ± standard error. Oneway analysis of variance (ANOVA) was used to compare the values between the four experimental animal groups to show the statistical significance difference. Statistical significance was assumed when P was less than 0.05.

Results

Hemodynamic monitoring & physiologic parameters

Mean arterial pressure (MAP) and heart rate for the 4 experimental animal groups at different time points are summarized in **Table 1** (i.e. 5 min before CPB, 30, 60, 120 min after the onset of CPB, and 30, 60 min during the recovery postoperative period). The MAP and heart rate in the placebo group were statistically lower than that in the sham-operated control group after CPB (all P < 0.05). However, there was no significant difference in regard to MAP and heart rate between the placebo group and the S1 and S5 groups (all P < 0.05), suggesting that the administration of sufentanil had no discernible effect on the hemodynamic parameters during CPB. The MAP and heart rate recovered to normal ranges 60 min after CPB disengagement.

The pH, blood gas (PaO_2, $PaCO_2$), lactate concentration (Lac, mmol/L) and hematocrit measurements at various time points (i.e. 5 min

Table 2. Physiologic measurements

Index	Group	Pre-CPB 5 min	CPB 60 min	Post-CPB 30 min	Post-CPB 60 min
pH	Sham-operated	7.416±0.050	7.414±0.048	7.413±0.045	7.418±0.042
	Placebo	7.404±0.049	7.386±0.033	7.335±0.019**	7.380±0.017*
	S1	7.419±0.047	7.396±0.040	7.366±0.023**	7.371±0.026*
	S5	7.411±0.042	7.389±0.044	7.363±0.021**	7.378±0.029*
PaO_2 (mmHg)	Sham-operated	357.6±30.3	359.4±32.1	358.5±31.4	328.5±34.0
	Placebo	362.1±28.1	374.5±30.1	356.5±25.9	281.5±29.1
	S1	357.3±30.7	369.1±28.5	314.1±24.2	306.0±22.2
	S5	355.3±29.2	364.6±27.1	316.7±22.9	308.0±24.1
$PaCO_2$ (mmHg)	Sham-operated	9.6±4.2	39.4±3.7	39.1±4.0	39.3±3.8
	Placebo	41.4±4.1	38.6±3.7	38.9±2.6	38.6±2.6
	S1	40.6±4.2	39.8±3.0	38.0±2.5	37.6±3.0
	S5	40.2±4.3	39.5±3.2	38.5±2.8	37.1±3.5
Lac (mmol/L)	Sham-operated	4.09±0.31	4.05±0.34	4.07±0.32	4.06±0.33
	Placebo	4.13±0.36	4.45±0.38	6.21±0.80**	5.33±0.51*
	S1	4.06±0.39	4.41±0.35	6.09±0.41**	5.24±0.53*
	S5	4.08±0.35	4.42±0.37	6.11±0.43**	5.27±0.55*
Hct (%)	Sham-operated	42.74±5.17	41.44±4.65	38.63±3.82	36.91±3.86
	Placebo	41.16±4.62	25.93±1.93**	26.13±1.84**	26.14±1.77**
	S1	41.51±4.75	26.34±1.67**	26.69±1.43**	26.98±1.63**
	S5	41.48±4.69	26.42±1.59**	26.87±1.66**	26.54±1.71**

Arterial blood pH, PaO_2, $PaCO_2$, Lactate, and Hct were measured 5 min before CPB, 60 min after the onset of CPB, and 30, 60 min after CPB disengagement (n = 6, CPB & non-CPB). Compared to the sham-operated group, *P < 0.05; **P < 0.01.

before CPB, 60 min after the onset of CPB, and 30, 60 min during the recovery postoperative period) are summarized in **Table 2**. The physiologic parameters in the sham-operated group were maintained within normal ranges throughout. The pH and lactose measurements were slightly lower in the placebo group as well as in the S1 and S5 groups after CPB procedure compared to the sham-operated group. Although the $PaCO_2$ values were similar among the 4 experimental animal groups and maintained within normal ranges in this study, the PaO_2 in the placebo group and the S1 and S5 groups dropped approximately 6-14% in 60 min after CPB disengagement. However, the PaO_2 in all 4 groups seemed to be stabilized during the CPB procedure. On the other hand, although the mean HCT values in the placebo group were consistently comparable to the S1 and S5 groups at all the four time points, the average HCT values in these 3 groups were 35% lower than the sham-operated group during and after CPB procedure (P < 0.01).

Cerebral water content (CWC) measurement

Neurologic injuries occur frequently in patients after exposure to an abnormally high level of cerebral microemboli during CPB [9]. Correlation has been identified between cerebral embolic load and cerebral edema inflicted by CPB procedure. Since an increased embolic load is responsible for cerebral water content increase (CWC) during CPB [9], we measured CWC in this study to determine whether sufentanil would alleviate cerebral edema in CPB. CWC (%) in the right hemisphere increased approximately 10.25% (P < 0.05) in the placebo group 1 hour after CPB procedure (86.12± 2.49%; range, 83.63% to 88.16%) compared to the sham-operated group (78.15±1.61%; range, 76.54% to 79.76%) (**Table 3**). However, for all the sufentanil-treated animals (i.e. S1 and S5 groups), CWC level significantly decreased compared to the placebo group (P < 0.05). As shown in **Table 3**, the mean CWC values in the right hemisphere (%) were 80.03±1.74% (range, 78.29% to 81.77%) for the S1 group, and 82.36±1.53% (range, 80.83% to 83.89%) for the S5 group, respectively. This demonstrated that CWC in the right hemisphere (%) was increased merely ~2.56% in the S1 group (P > 0.05), and ~5.13% (P < 0.05) in the S5 group, respectively compared to the sham-operated control group.

Table 3. Measurements of cerebral water content (CWC), cerebral calcium accumulation, as well as S-100β protein levels in the serum

Groups	The dose of sufentanil ($\mu g \cdot kg^{-1}$)	Cerebral water content (CWC) (%)	S100β in the serum ($pg \cdot ml^{-1}$)	Cerebral calcium accumulation ($\mu g \cdot g^{-1}$)
Sham-operated	N/A	78.15±1.61	309.55±36.24	64.03±13.19
Placebo	N/A	86.12±2.49*	561.03±71.28*	112.86±11.76*
S1	1	80.03±1.74Δ	429.62±45.89*,Δ	77.00±13.26*,Δ
S5	5	82.36±1.53*,Δ,#	452.66±39.67*,Δ	83.9±10.32*,Δ

Compared to the sham-operated group, *$P < 0.05$; compared to the placebo group, Δ$P < 0.05$; compared to the S1 group, #$P < 0.05$.

Cerebral calcium measurement

The cerebral calcium ion homeostasis Impairment usually occurs in neuronal degeneration and cell death after ischemic CNS injury [9]. Studies have reported Ca^{2+} influx increase in fluid-percussion brain injury, [17] or cortical contusion [18]. Meanwhile, the increase of mitochondrial Ca^{2+} uptake, activation of calcium-dependent neutral proteases such as calpain has also been detected in the injury [9]. It has been revealed in several studies of cerebral ischema that the increase of calpain proteolytic activity may contribute to the degradation of cytoskeletal proteins such as spectrin, microtubule-associated protein 2, and neurofilament proteins [6, 19]. In contrast, calpain inhibitor administration is neuroprotective in the rat with cortical impact injury or lateral fluid-percussion brain trauma [1, 20, 21]. Here, we sought to measure the total calcium concentration in the rat brain to evaluate the effect of sufentanil on the cerebral calcium accumulation associated with CPB. The total cerebral calcium concentration in the left hemisphere (mg/g of wet weight) was increased dramatically by ~76.26% in the placebo group within 1 hour after CPB disengagement (112.86± 13.19%; range, 101.10% to 124.62%) compared to the sham-operated group (64.03± 13.19%; range, 50.84% to 77.22%) (**Table 3**). However, when animals were preexposed to sufentanil or continuously administrated with sufentanil during CPB, cerebral calcium concentration was significantly decreased compared to the placebo group. As shown in **Table 3**, the mean values of the total cerebral calcium concentration in the left hemisphere were 77.00±13.26% (range, 63.74% to 90.26%) for the S1 group, and 83.90±10.32% (range, 73.58% to 94.22%) for the S5 group, respectively. Thus, the total cerebral calcium concentration in the left hemisphere was increased merely by ~20.31% in the S1 group, and by ~29.70% in the S5 group compared to the sham-operated control group, respectively.

Examination of S-100β protein levels in the plasma

As shown in **Table 3**, the mean value of S-100β levels was significantly higher in placebo group than in the sham-operated group ($P < 0.05$). These data indicated that CPB was responsible for the dramatic increase of neuronal cell death in the brain and the subsequently elevated cerebral dysfunction. There was ~81% increase in the plasma S-100β levels: the average S-100β levels in the placebo group was 561.03±71.28 pg/ml compared to 309.55± 36.24 pg/ml in the sham-operated group. However, when animals were preadministered with sufentanil and continuously exposed to sufentanil during CPB, plasma S-100β levels were substantially reduced in the S1 and S5 groups compared to the placebo group ($P < 0.05$): the average S-100β concentration was 429.62±45.89 pg/ml in the S1 group and 452.66±39.67 pg/ml in the S5 group, respectively. The average plasma S-100β concentration was reduced to 39-46%, significantly lower than the ~81% increase in the placebo group. These results suggest that sufentanil treatment is potentially neuroprotective against cerebral malfunction induced by neuronal cell death in CPB.

Discussion and conclusion

In this study, we examined several parameters in the experimental animals treated with sufentanil during CPB. These parameters are usually monitored for evaluating potential neurologic damages associated with CPB. We would like

to determine here whether sufentanil treatment before and during CPB would alleviate neurologic injuries. In our study, in rats treated with sufentanil (i.e. the S1 and S5 groups), the level of cerebral water content (CWC) significantly reduced compared to the placebo group. This is consistent with other study that embolic load increase is responsible for the CWC increase during surgery [5, 22]. Similarly, a dramatic increase in embolic load usually induces cerebral edema-associated neurologic injuries [23-25]. Thus, an increase in CWC indicates a higher level of cerebral microemboli exposure, and potentially more severe neurologic damages. Therefore, our study demonstrated that sufentanil can partially relieve CPB-induced cerebral edema in CWC increase although the underlying mechanism is not clear at this stage [22]. Embolic event counting will determine whether the reduction of CWC increase during sufentanil treatment is associated with microemboli exposure [22]. In addition, when animals were continuously treated with sufentanil during CPB, the cerebral calcium level was significantly lower than the placebo group. The reduced cerebral calcium level indicates a decreased activation of calcium-dependent neutral proteases such as calpain and cytoskeletal proteins [26]. Similarly, plasma S-100β levels in the S1 and S5 groups were lower than that in the placebo group, suggesting that sufentanil treatment potentially reduces neuronal cell death in CPB [10, 11, 16].

Previous studies indicated that CPB brain injury may vary, depending on the level of anesthesia (e.g. none, chloral hydrate, or isoflurane) delivered during the surgery [27, 28]. However, in the anesthesia regimen, chloral hydrate but not isoflurane can impair the learning and memory abilities after CPB in rats. Importantly, isoflurane administration has potential neuroprotective effects against celebral ischemia and celebral injury, such as ameliorated short-term neurocognitive impairment associated with CPB [29, 30]. This is probably because that cerebral cholinergic system is involved. Cerebral cholinergic system is a critical in cortical and hippocampal plasticity, where its disruption abolishes learning and memory potentiation [6]. For example, eptazocine, an agonist for opioid kappa-receptors, elicited its cerebral protective effect via binding to opioid kappa-receptors and subsequently activating the central cholinergic system [6, 19]. Therefore, our further studies will involve determining whether the neuroprotective effects of sufentanil is associated with cerebral cholinergic pathway.

Additionally, Our future study also includes investigating the potential the roles of sufentanil administration in a recovery CPB rat model, such as Morris Water Maze Task test (an indicator of visual-spatial learning and memory), which has been widely employed to measure the levels of neurocognitive impairments [10, 16]. Also, it is worth mentioning that Sufentanil is a reliable anagesic component for anesthetic regimen, where no severe intrinsic neurotoxicity has been identified in clinical settings [8, 15]. Importantly, sufentanil has no difficulties in passing across the blood-brain barrier [12, 15]. Conclusively, sufentanil may represent a potentially promising candidate as a neuroprotectant for preemptive use in alleviating of CBP-associated brain injury in clinical settings.

Acknowledgements

This study was supported by the Scientific & Technological Advancement Grant in 2013 from the city government of Jingzhou, Hubei, China.

Disclosure of conflict of interest

None.

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