Journal of Clinical and Experimental Cardiology

Nan et al., J Clin Exp Cardiolog 2018, 9:3
DOI: 10.4172/2155-9880.1000576

Research Article

Open Access

Propofol Prevents Thrombosis in a Rat Common Carotid Artery Thrombosis Model

Yongshan Nan[1], **Haiying Jiang**[2], **Xianglan Jin**[1], **Xiang Li**[3], **Chunzi Jin**[3] **and Xianwu Cheng**[3*]

[1]*Department of Anesthesiology, Yanbian University Hospital, Yanji 1330, Jilin, P.R. China*

[2]*Department of Physiology and Pathophysiology, Jiaxing University Medical College, Jiaxing 314001, Zhejiang, P.R. China*

[3]*Department of Cardiology, Yanbian University Hospital, Yanji 133000, Jilin, P.R. China*

[*]**Corresponding author:** Xianwu Cheng, Department of Cardiology, Yanbian University Hospital, Juzijie 1327, Yanji 133000, Jilin, P.R. China, Tel: +86-15526770371; E-mail: xianwu@med.nagoya-u.ac.jp

Received date: March 08, 2018; **Accepted date:** March 15, 2018; **Published date:** March 19, 2018

Copyright: ©2018 Nan Y, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Aim: The aim of this study was investigated the beneficial effect of propofol on thrombosis in a rat carotid artery thrombosis model.

Methods and Results: Sprague-Dawley rats underwent iron chloride3 ($FeCl_3$)-induced carotid artery thrombosis model surgery were treated with vehicle (M group), low- (PL group), middle- (PM group) or high-dose propofol (PH group). Rats were received sham operation served as control (C group). As compared with the M group, propofol treatment significantly inhibited thrombus weights and improved the degree of embolization. Propofol also markedly improved blood CD62P intensity. Moreover, as compared with C group rats, the levels of plasma TXA2, PGI2, t-PA, t-PA/PAI-1 ratio, and P-selectin were harmful altered in M group rats in response to $FeCl_3$ induction; these effects were improved in the PL and/or PM and PH groups.

Conclusions: These findings suggested that the beneficial anti-thrombotic effect of propofol is likely attributable, at least in part, to attenuation of the endothelia injury, platelet activation and fibrinolytic inactivation induced by $FeCl_3$ in a rat carotid artery thrombosis model.

Keywords: Propofol; Thrombosis; TXA2; animal model

Introduction

Thrombotic disease is a major healthy concern world-wide. The formation of thrombosis is a key vent in the pathogenesis of stroke, acute myocardial infarction, and other ischemic conditions that includes the most comment and growing causes of morbidity and mortality [1,2]. Thrombosis is one target of interest, and antithrombotic strategies to reduce the risk of death, stroke, or myocardial infarction have been tested in several randomized trials [3,4]. Many attempts (including nutritional and pharmacological approaches) prevent thrombosis and thromboembolism has been proposed that are directed at reversing hypercoagulability and stasis [3-5]. Despite the advances that have been achieved, limited useful drugs are currently in clinical practice that mitigates arterial thrombosis.

Thrombosis can be divided into two pathological processes: thrombosis formation and thromboembolism. Thrombosis refers to the pathological process where visible blood components coagulate and form emboli, block blood vessels, cause obstructions in the corresponding parts of blood flow, and result in ischemia and hypoxia of the surrounding tissues or organs in response to specific stimuli [6]. The etiology and mechanism of thrombosis are very complex because a variety of pathophysiological conditions can affect thrombosis formation, such as vascular endothelial injury, platelet activity and quantity changes, increased blood coagulation, decreased anticoagulant or fibrinolytic activity, and hemorheological abnormalities.

Because propofol is a short-acting intravenous anesthetic that has a rapid onset, smooth induction, and fewer side effects, it is widely used in clinical practice. Propofol has an anesthetic effect and it also has many non-narcotic effects, such as antiemetic, analgesic, immune regulation, brain protection, anti-platelet aggregation, and antioxidant effects [7-9]. Chung et al. [9] reported that the clinical dose of propofol can inhibit platelet aggregation. Platelet aggregation plays a key role in the thrombosis process, indicating that propofol may also have an impact on thrombosis formation. Recent few clinical studies have shown that propofol has a beneficial effect on perioperative hemorheology of colon cancer patients [10]. In this study, whole blood viscosity and plasma viscosity decreases to different degrees at 30 min and 90 min after propofol induction compared with before anesthesia, which can reduce the risk of thrombosis formation in patients. However, the propofol-mediated anti-thrombotic benefits remain unclear.

Here, we established the rat carotid artery thrombosis model to examine the effect of propofol on thrombosis formation, and try to explore its possible mechanism by which the endothelial repair, platelet inactivation and fibrinolytic inactivation might contribute to the anti-thrombotic benefit.

Citation: Nan Y, Jiang H, Jin X, Li X, Jin C, et al. (2018) Propofol Prevents Thrombosis in a Rat Common Carotid Artery Thrombosis Model. J Clin Exp Cardiolog 9: 576. doi:10.4172/2155-9880.1000576

Materials and Methods

Antibodies and regents

Propofol was purchased from AstraZeneca UK Ltd. ELISA kits (Shanghai Yanjin Biotechnology Co., Ltd). The enzyme-linked immunosorbent assay (ELISA) kits for thromboxane A2 (TXA2), prostaglandin I2 (PGI2), P-selectin, tissue-type plasminogen activator (t-PA), and plasminogen activator inhibitor-1 (PAI-1) were purchased from R&D Systems (Minneapolis, MN). CD62P antibody (FITC) reagents and CD61 antibody (PE) reagents were purchased from BD Biosciences (Bedford, MA).

Animals

We used 8-week-old Sprague–Dawley rats (n=50, 250–300 g; Yanbian University Experimental Animal Center, Yanji, China) in this experiment. The animal protocols were approved by the Institutional Animal Care and Use Committee of Yanbian University Graduate School of Medicine and performed according to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health.

Rat model of carotid artery thrombosis

Rat carotid artery thrombosis model was created as previously described [11]. In brief, the animals were anesthetized with an intraperitoneal injection of 20% urethane (7 mg/kg) and puncture catheterized *via* a 24 trocar on the tail vein to connect the saline dripping for the administration of vehicle and propofol in later. Following exposure and crippled the right carotid artery with a dissection clamp, the arteries were wrapped with the filter paper containing saturated 20% $FeCl_3$ solution and were then started to infuse the saline or propofol into the rats for the indicated time points, respectively. We removed the $FeCl_3$ filter strip after applying it for 15 min (the surgical towel was kept in place) and the color of the right common carotid artery wall had darkened; after 45 min, we ligated both ends of the filter strip using suture thread, according to the length of the filter strip, to cut the blood vessel accurately. The rats underwent sham-operation (the right common carotid artery was wrapped with filter paper containing normal saline) were received saline infusion as control rats (C group). We isolated arterial samples from each group, fixed them in 4% formalin for 24 h, washed them with phosphate-buffered saline water for 24 h, and placed them in 70% ethanol for HE staining. We blotted the remaining blood vessels using extra filter paper, and weighed them using the electronic balance. The blood was collected from the rat heart and divided to the tubes for the flow cytometry (100 µL). The remaining blood was centrifuged at 3000 r/min for 15 min, and the plasma was collected and stored it in a −80°C freezer for ELISA.

Experimental treatments

The Sprague-Dawley rats underwent carotid artery thrombosis model surgery were assigned to one of 4 groups (n=10 for each group) as follows: vehicle (M group), propofol low-dose (PL group), propofol middle-dose (PM group), and propofol high-dose (PH group). The PL, PM, and PH groups were continuously infused at a rate of 4, 8, and 16 mg/kg/h, respectively, with propofol diluted in saline via the tail vein. The rats received sham-operation were continuously infused with 0.9% saline at a rate of 1 ml/h as control rats (C group). The infusion was continued for 1 h in all five groups.

Morphological analyses

The fixed common carotid artery was dehydrated in ethanol, embedded in paraffin, and cut into 4-µm thick slices. For the HE staining process, the treated slices were immersed in hematoxylin solution staining for 15 min, placed into 1% hydrochloric acid ethanol and ammonia ethanol for several seconds for color separation, and rinsed with running water for 1 h. They were then placed into distilled water for about 5 min, followed by 70% and 90% alcohol to dehydrate for 10 min. Eosin stain (1%) was then added for 3 min. The stained slices were dipped into ethanol from low to high concentrations, and then immersed in xylene to make the slices transparent. After removing the slices, the resin was dropped onto a slide and covered with coverslips. After the resin solidified, the pathological changes to the common carotid artery were observed under a microscope.

Flow cytometry detection of platelet activation

Into each of the subgroup-labeled 1.5 ml centrifuge tubes, 2 µl of CD61-PE and 2 µl of CD62P-FITC antibodies were added, followed by 5 µl of whole blood. The tube was shaken gently to mix, placed in the dark for 20 min at room temperature, and 1 ml of pre-cooled 1% paraformaldehyde solution was added, mixed until even, and placed into the dark for 30 min at 2–8°C. The flow cytometer was used for detection, and measured data were analyzed and processed in accordance with the software that accompanied the flow cytometer.

ELISA detection of plasma biochemical markers

The levels of plasma TXA2, PGI2, P-selectin, t-PA, and PAI-1 were detected using ELISA, according to the manufacturer’s instructions.

Statistical methods

The data are expressed as the mean ± standard diviation (SD) in all analyses. A one-way analysis of variance (ANOVA) for comparisons of three or more groups followed by Tukey's post hoc tests was used for the statistical analyses. SPSS software ver. 17.0 (SPSS, Chicago, IL) was used for all statistical analyses. P-values <0.05 were considered significant.

Results

Effect of propofol on thrombus weight and morphological changes

Carotid artery thrombosis results for each group are shown in Figure 1. The control group had no thrombosis. Compared with the M group, propofol treatment inhibited thrombus weights in a dose-dependent manner. As shown in Figure 2, the control rats had no thrombus in the carotid artery: the lumen was unobstructed and the vascular endothelium was continuous. In M group, the arteries were filled with mixed thrombi composed of platelets, red blood cells, and a small amount of white blood cells. The thrombi were tight and firm, blocked the entire lumen. PL and PM rats exhibited decreased in the thrombus: the thrombosis was loose. Propofol treatment at high-dose markedly reduced intra-arterial thrombosis: the thrombus was loose, vascular endothelial cells were slightly shedding, and the endometrium was more complete (Figure 2).

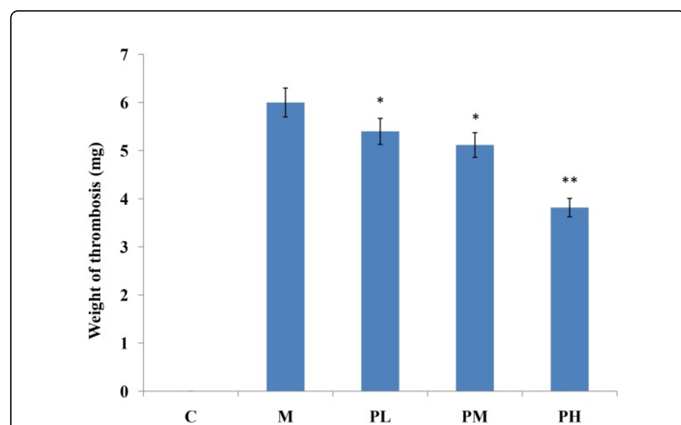

Figure 1: Effect of propofol on carotid artery thrombosis in rats; Compared with the model group; * indicates P<0.05; ** indicates P<0.01; Control group (C); the model group (M); the propofol low-dose group (PL); the propofol middle-dose group (PM); and the propofol high-dose group (PH).

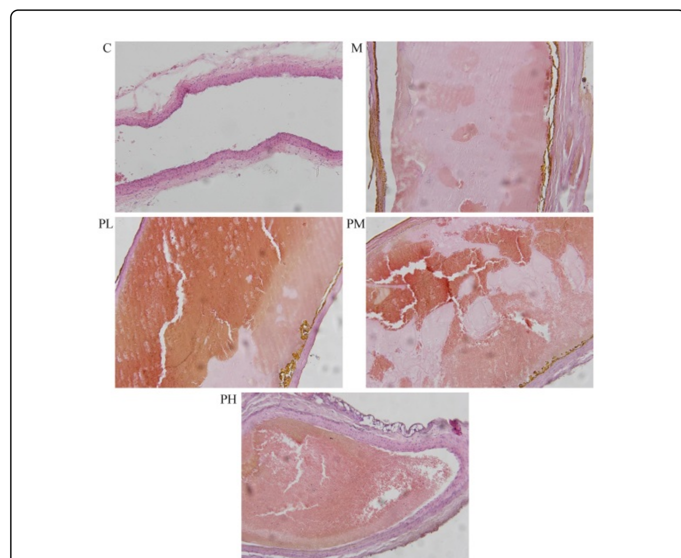

Figure 2: Results of HE staining of the common carotid artery in rats (× 200); Control group (C); the model group (M); the propofol low-dose group (PL); the propofol middle-dose group (PM); and the propofol high-dose group (PH).

Effect of propofol on platelet activation

The mean fluorescence intensity of the platelet activation marker CD62P in the model group was significantly higher than that in the control group (P<0.01) (Table 1, Figure 3). As anticipated, propofol significantly improved increased CD62P mean fluorescence intensity in a dose-dependent manner, suggesting that pharmacological therapy with propofol prevented platelet activation in response to $FeCl_3$ induction.

Group	Dose of propofol (mg/kg/h)	n	CD62P (fluorescence intensity)
C	—	10	328.4 ± 28.1
M	—	10	1068.2 ± 153.3$^{\#\#}$
PL	4	10	567.0 ± 90.7$^{\#\#**}$
PM	8	10	392.1 ± 62.8$^{\#**}$
PH	16	10	355.5 ± 27.9$^{\#**}$

Table 1: Effect of propofol on CD62P level; Compared with the control group, $^{\#}$ -indicates P<0.05; $^{\#\#}$ -indicates P<0.01; compared with the model group, ** -indicates P<0.01; Control group (C); the model group (M); the propofol low-dose group (PL); the propofol middle-dose group (PM); and the propofol high-dose group (PH).

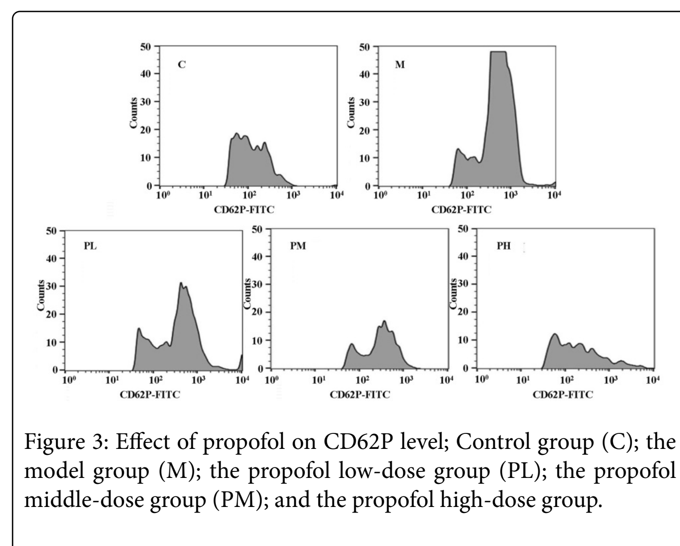

Figure 3: Effect of propofol on CD62P level; Control group (C); the model group (M); the propofol low-dose group (PL); the propofol middle-dose group (PM); and the propofol high-dose group.

Effects of propofol on plasma TXA2, PGI2, and P-selectin

As shown in Table 2, the M group had increased levels of plasma TXA2 and P-selectin and decreased levels of plasma PGI2 as compared to control group (P<0.01). Compared with the model group, the TXA2 levels in the middle- and high-dose groups were significantly decreased (P<0.01). The P-selectin level in the different propofol dose groups was decreased to varying degrees, while the PGI2 level in the middle- and high-dose groups was significantly increased (P<0.05, P<0.01).

Group	Dose of propofol (mg/kg/h)	TXA2 (ng/L)	PGI2 (ng/L)	P-selectin (ng/L)
C	—	12.00 ± 2.08	27.17 ± 2.89	3.22 ± 0.30
M	—	44.88 ± 3.62$^{\#\#}$	19.10 ± 2.08$^{\#\#}$	4.56 ± 0.37$^{\#\#}$
PL	4	41.69 ± 2.36$^{\#\#}$	20.84 ± 1.74$^{\#\#}$	4.16 ± 0.31$^{\#\#*}$
PM	8	30.42 ± 3.90$^{\#\#**}$	21.62 ± 2.49$^{\#\#*}$	3.78 ± 0.19$^{\#\#**}$
PH	16	24.92 ± 3.43$^{\#\#**}$	24.23 ± 1.26$^{\#**}$	3.43 ± 0.39**

Table 2: Effects of propofol on plasma TXA2, PGI2 and P-selectin; Compared with the control group, $^{\#}$ -indicates P<0.05; $^{\#\#}$ -

indicates P<0.01; Compared with the model group, * -indicates P<0.05; and ** -indicates P<0.01; Control group (C); the model group (M); the propofol low-dose group (PL); the propofol middle-dose group (PM); and the propofol high-dose group (PH).

Effects of propofol on plasma t-PA and PAI-1

Compared with the control group, the t-PA content in the model group was significantly decreased and the mean value of the PAI-1 contents was increased without significant difference, while the t-PA/PAI-1 ratio was significantly decreased (Table 3). As shown in Table 3, propofol significantly improved the changes in the levels of plasma t-PA in a dose-dependent manner. However, the changes in the levels of plasma PAI-1 were only significantly mitigated in the PM and PH groups. Interestingly, propofol improved the t-PA/PAI-1 ratio in a dose-dependent manner.

Group	Dose of propofol	t-PA	PAI-1	t-PA/PAI-1
	(mg/kg/h)	(ng/L)	(ng/L)	
C	—	1123.69 ± 69.96	21.25 ± 0.82	52.88 ± 4.43
M	—	897.99 ± 52.86##	23.47 ± 1.82#	37.26 ± 3.27##
PL	4	978.30 ± 65.35**	22.38 ± 1.70	44.67 ± 1.46**
PM	8	1011.23 ± 52.48**	21.08 ± 1.97*	46.27 ± 5.37**
PH	16	1059.45 ± 66.99**	20.95 ± 1.27**	49.80 ± 6.16**

Table 3: Effects of propofol on plasma t-PA and PAI-1; Compared with the control group, # -indicates P<0.05; ## -indicates P<0.01; Compared with the model group; * -indicates P<0.05; and ** -indicates P<0.01; Control group (C); the model group (M); the propofol low-dose group (PL); the propofol middle-dose group (PM); and the propofol high-dose group (PH).

Discussion

In this study, the rat carotid artery thrombosis model was established using the ferric chloride etching method [12-14]. $FeCl_3$ solution was applied to the right common carotid artery in the rats, so that the vascular endothelial cell junction sites were separated and exfoliated and collagen was exposed. Iron ions enter into the arterial lumen and iron ions with a high positive charge can lead to the oxidative damage of vascular endothelium, causing platelet activation, aggregation, and activation of the coagulation system, leading to thrombosis. HE staining also showed common carotid artery thrombosis. Thrombus weight and HE staining results showed that thrombus weights in the propofol groups at different concentrations were decreased, and the degrees of vascular occlusion and vascular endothelium exfoliation were relatively reduced, indicating that propofol can inhibit thrombosis formation and that it has a protective role in the blood vessel endothelium.

Platelets have a critical role in the process of thrombus because thrombi are not formed without platelets [15]. When the blood vessel is injured, the subendothelial collagen is exposed, which can promote platelet activation, cause platelet adhesion, aggregation, and release reaction. Platelet activation and aggregation play a key role in the development and progression of thrombotic diseases. Detecting platelet activation and platelet aggregation can accurately reflect platelet activity [16]. A variety of platelet activation markers have been discovered recently [17], such as platelet P-selectin, platelet factor 4 (PF4), β-thromboglobulin, platelet glycoprotein V, and platelet GPIIb/IIIa. P-selectin, also known as platelet activation-dependent granule surface membrane protein or CD62P, is a glycoprotein with the relative molecular weight of 140 KD, which is also known as GMP140. It is present in the Weibel-Palade bodies of platelet α particles and endothelial cells, with little expression on the platelet surface in healthy people. When platelets are activated, CD62P can quickly transfer from the cytoplasm to the cell surface, so that platelets adhere to white blood cells and endothelial cells. The increase in CD62P expression is a specific and sensitive indicator of platelet activation, and thus, it is a gold standard to determine platelet activation [18-19]. CD62P levels were measured using flow cytometry, and the mean fluorescence intensity of CD62P in the model group was significantly higher compared with the control group. However, the mean fluorescence intensity of CD62P in the drug group was significantly weaker compared with the model group, and the difference was more significant in the high-dose group. This indicates that propofol can inhibit platelet activation, and with an increasing dose of propofol, the inhibitory effect also increased. Plasma P-selectin content was determined using the ELISA method, which confirmed the conclusion that propofol has a role in anti-platelet activation and that it can also inhibit platelet aggregation.

Dordoni et al. [20] suggested that propofol at concentrations required for sedation and general anesthesia has no inhibitory effect on platelet aggregation after 3 h of incubation. However, Fourcade et al. [21] showed that a propofol emulsion produced similar inhibition of platelet aggregation because inhibition induced by lysophosphatidic acid, platelet-activating factor, and TXA2 occurred in a dose-dependent manner. The TXA2 pathway is a major contributor to amplification of the initial platelet activation process. TXA2 mediates its effect through the thromboxane prostanoid receptor that is expressed in platelets and also in endothelial cells, macrophages, and monocytes, and it thus contributes to the development of atherosclerotic lesions [22].

The TXA2 content in the model group was significantly increased, while the PGI2 content was significantly decreased. Compared with the model group, the TXA2 contents in the propofol high- and middle-dose groups were significantly decreased, while the PGI2 content in the high-dose group was significantly increased. TXA2 is not stored in platelets, and when certain stimuli act on platelets, they can be activated. Activation of phospholipase A2 within platelets and subsequently stimulates the membrane phospholipid to release arachidonic acid that is present on the cell membrane in the form of phospholipids, which generates unstable prostaglandin G2 (PGG2) and prostaglandin H2 (PGH2). First, under the action of cyclooxygenase, PGH2 generates TXA2 under the action of platelet thromboxane synthase within platelets, and PGH2 generates PGI2 under the action of prostacyclin synthase in the vascular endothelial cells [22,23]. TXA2 can reduce the platelet cAMP concentration, and it also has a strong role in platelet aggregation and blood vessels contraction. Additionally, TXA2 also promote thrombosis formation. PGI2 has an opposite role: it can increase platelet cAMP content, has a role in inhibiting platelet aggregation and relaxing blood vessels, and can inhibit thrombosis formation [24,25]. There is a dynamic balance between TXA2 and PGI2, which plays a key role in the regulation of platelet function, vessel wall contraction, and vascular wall cell migration and growth, and it is significant in the maintenance of intravascular environment stability. When propofol (8 and 16

mg/kg/h) is used to treat rats, it can inhibit platelet production of TXA2 and promote endothelial cell production of PGI2, thereby destroying the balance between TXA2 and PGI. Propofol also plays a role in inhibiting thrombosis; this may be related to the role of propofol in inhibiting platelet activation and protecting vascular endothelial cells.

There is a strong link between thrombotic disease and fibrinolytic system function. Fibrinolysis is a fibrin degradation process in the blood coagulation process that involves a series of chemical reactions in the fibrinolytic system. The fibrinolytic system includes plasminogen; plasminogen activator (such as tissue-type plasminogen activator [t-PA], urine plasminogen activator) and plasminogen activator inhibitor (such as PAI-1); and plasmin and plasmin inhibitors (such as α 2-antiplasmin). In the normal state, only inactive plasminogen is present in the plasma, but when the coagulation system is activated, fibrin is formed. The fibrinolysis system in the plasma is then activated, and plasminogen activator secretion is increased so that plasminogen is transformed into active plasmin, which breaks down fibrin and plays a role in thrombolysis. t-PA is a type of plasminogen activator produced by the vascular endothelial cells. It is an important factor that induces fibrinolytic activation and promotes thrombolysis in vivo. When fibrin is formed, it can cause an acute release of t-PA, and because PAI-1 is a major inhibitor of t-PA, it can quickly act on the plasma-free t-PA and produce complexes, thereby inhibiting t-PA activity. Plasminogen activation and fibrin degradation processes are regulated using t-PA and PAI-1 complex formation [26–28]. If this system is unbalanced, it can cause local micro-thrombosis, and ultimately lead to thrombotic disease. Therefore, this imbalance plays a vital role in thrombotic diseases.

Our results showed that the t-PA content in the model group was significantly decreased compared with the control group, which may be because of a large t-PA aggregation on the thrombus surface after thrombosis formation that is specifically adsorbed by the thrombus. t-PA release was also reduced because of the destruction of a large amount of vascular endothelial cells. Compared with the model group, the t-PA contents in the propofol groups were increased, indicating that propofol has a protective effect on vascular endothelial cells and can promote an acute release of t-PA. There was no significant change of the PAI-1 level between the model group and the control group, indicating that the $FeCl_3$-induced thrombus model does not cause changes in plasma PAI-1. Additionally, the t-PA/PAI-1 ratio was decreased, which is consistent with results of other studies [29]. Compared with the model group, the PAI-1 levels in the high- and middle-dose propofol groups were significantly decreased, and propofol is likely to inhibit PAI-1 production. Thus, propofol has a protective effect on vascular endothelial cells, and thrombus formation is inhibited by increasing the t-PA level and decreasing the PAI-1 level, which adjusts the t-PA/PAI-1 balance to increase the fibrinolytic system activity.

In summary, propofol has a role in thrombosis inhibition at a high concentration. Propofol modulates the t-PA/PAI-1 balance by increasing the t-PA level and decreasing the PAI-1 level to promote fibrinolysis, thereby inhibiting thrombus formation. However, propofol also inhibits platelet production of TXA2 and promotes vascular endothelial cell production of PGI2, thus destroying the balance between TXA2 and PGI2 and playing a role in inhibiting thrombus formation.

Acknowledgment

This study was supported by the National Natural Science Foundation of China (No. 81460082, 81560240, 81660240, and 81770485).

References

1. Koupenova M, Kehrel BE, Corkrey HA, JE Freedman (2017) Thrombosis and platelets: an update. Euro Heart J 38: 785-791.
2. Zannad F, Stough WG, Regnault V, Gheorghiade M, Deliargyris E, et al. (2013) Is thrombosis a contributor to heart failure pathophysiology? Possible mechanisms, therapeutic opportunities, and clinical investigation challenges. Int J Cardiol 167: 1772-1782.
3. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, et al. (2017) Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 377: 1319-1330.
4. Resor CD, Nathan A, Kereiakes DJ, Yeh RW, Massaro JM, et al. (2016) Impact of Optimal Medical Therapy in the Dual Antiplatelet Therapy Study. Circulation 134: 989-998.
5. Lamberts M, Gislason GH, Lip GY, Lassen JF, Olesen JB, et al. (2014) Antiplatelet Therapy for Stable Coronary Artery Disease in Atrial Fibrillation Patients Taking an Oral Anticoagulant. Circulation 129: 1577-1585.
6. Furie B, Furie BC (2008) Mechanisms of thrombus formation. N Engl J Med 359: 938-949.
7. Fan W, Zhu X, Wu L, Wu Z, Li D, et al. (2015) Propofol: an anesthetic possessing neuroprotective effects. Eur Rev Med Pharmacol Sci 19: 1520-1529.
8. Vasileiou I, Xanthosa T, Perrea D, Koudouna E, Klonaris C, et al. (2009) Propofol: a review of its non-anaesthetic effects. Eur J Pharmacol 605: 1-8.
9. Chung HG, Myund SA, Son HS, Yun HK, Jin N, et al. (2013) In vitro effect of clinical propofol concentrations on platelet aggregation. Artif Organs 37: E51-55.
10. Chen J, Wang LJ (2015) The Effects of sevoflurane and propofol anesthesia in patients undergoing radical perioperative blood rheology on colon cancer. Pract J Cancer 30: 929-931.
11. Jin M, Jin G, Huang W, Gao Z (2017) PEGylation of Lumbrokinase improves pharmacokinetic profile and enhances antithrombotic effect in a rat carotid artery thrombosis model. Mol Med Rep 16: 4909-4914.
12. Qin YR, You SJ, Zhang Y, Li Q, Wang XH, et al. (2016) Hydrogen sulfide attenuates ferric chloride-induced arterial thrombosis in rats. Free Radic Res 50: 654–665.
13. Li W, Nieman M, Sen GA (2016) Ferric Chloride-induced Murine Thrombosis Models. J Vis Exp.
14. Li W, McIntyre TM, Silverstein RL (2013) Ferric chloride-induced murine carotid arterial injury: A model of redox pathology. Redox Biol 1: 50-55.
15. Cerletti C, Tamburrelli C, Izzi B, Gianfagna F, De GG (2012) Platelet-leukocyte interactions in thrombosis. Thromb Res 129: 263-266.
16. Frossard M, Fuchs I, Leitner JM, Hsieh K, VIcek M, et al. (2004) Platelet function predicts myocardial damage in patients with acute myocardial infarction. Circulation 110: 1392-1397.
17. Gurney D, Lip GY, Blann AD (2002) A reliable plasma marker of platelet activation: does it exist? Am J Hematol 70: 139-144.
18. Ay C, Jungbauer LV, Kaider A, Koder S, Panzer S, et al. (2008) P-selectin gene haplotypes modulate soluble P-selectin concentrations and contribute to the risk of venous thromboembolism. Thromb Haemost 99: 899-904.
19. Michels M, van der Ven AJ, Djamiatun K, Fijnheer R, Groot PGD, et al. (2012) Imbalance of angiopoietin-1 and angiopoetin-2 in severe dengue and relationship with thrombocytopenia, endothelial activation, and vascular stability. Am J Trop Med Hyg 87: 943-946.

20. Dordoni PL, Frassanito L, Bruno MF, Proietti R, Cristofaro RD, et al. (2004) In vivo and in vitro effects of different anaesthetics on platelet function. Br J Haematol 125: 79-82.

21. Fourcade O, Simon MF, Litt L, Samii K, Chap H (2004) Propofol inhibits human platelet aggregation induced by proinflammatory lipid mediators. Anesth Analg 99: 393-398.

22. Fontana P, Zufferey A, Daali Y, Reny JL (2014) Antiplatelet therapy: targeting the TxA2 pathway. J Cardiovasc Transl Res 7: 29-38.

23. Zhou W, Fang WR, Li YM (2014) Thromboxane A2- Novel target for drug treatment of ischemic stroke. Pharm Clin Res 22: 246-250.

24. Yuhki K, Kojima F, Kashiwagi H, Kawabe J, Fujino T, et al. (2011) Roles of prostanoids in the pathogenesis of cardiovascular diseases: Novel insights from knockout mouse studies. Pharmacol Ther 129: 195-205.

25. Liu H, Chang L, Chen Y, Xia S, Zhang X (2003) Clinical implication of the changes of cAMP, TXA2 and PGI2 in CSF of asphyxiated newborns. J HuazhongUniv Sci Technolog Med Sci 23: 195-197.

26. Longstaff C, Williams S, Thelwell C (2008) Fibrin binding and the regulation of plasminogen activators during thrombolytic therapy. Cardiovasc Hematol Agents Med Chem 6: 212-223.

27. Fugate JE, Rabinstein AA (2014) Update on intravenous recombinant tissue plasminogen activator for acute ischemic stroke. Mayo Clin Proc 89: 960-972.

28. Ji J, Ji SY, Yang JA, He X, Yang XH, et al. (2012) Ultrasound-targeted transfection of tissue-type plasminogen activator gene carried by albumin nanoparticles to dog myocardium to prevent thrombosis after heart mechanical valve replacement. Int J Nanomedicine 7: 2911-2919.

29. Tang YH, Liang Y, Yang J, Zhang SP, Deng CQ (2006) Changes of TXA2, PGI2, anticoagulant and fibrinolytic activity in plasma of FeCl3 induced carotid artery thrombosis in rats. Chinese Pharmacol Bull 22: 1353-1356.