Int J Clin Exp Med 2020;13(8):6099-6106
www.ijcem.com /ISSN:1940-5901/IJCEM0113450

Original Article

The Effect of leonurus japonicus injection on preventing postpartum hemorrhage after cesarean section and its influence on the protein expression of ROCK I and ROCK II

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Received April 28, 2020; Accepted June 1, 2020; Epub August 15, 2020; Published August 30, 2020

Abstract: Objective: To investigate the effect of leonurus japonicus injection on preventing postpartum hemorrhaging after cesarean section and its influence on the protein expression of Rho-associated kinase (ROCK) I and ROCK II. Methods: This study was performed in 106 parturients who were admitted to Ningbo Zhenhai People's Hospital for caesarean section from April 2017 to April 2018. According to a random number table, parturients were allocated to the oxytocin group and the leonurus japonicus group (53 patients in each group). Parturients in the oxytocin group were injected with oxytocin. In the leonurus japonicus group, parturients were given leonurus japonicus injection. Blood loss at 12 h and 24 h after operation, postpartum uterine contractility, routine blood indexes, coagulation function pre and post-surgery, including fibrinogen (FIB), D-dimer (D-D), activation part thrombin time (APTT), and thrombin time (TT), protein expression of ROCK I and ROCK II before and after operation, preventive effect, and adverse reactions were compared between the two groups. Results: Blood loss at 12 h and 24 h after operation in the leonurus japonicas group was less than those in the oxytocin group (both $P<0.01$). Postpartum uterine contractility in the leonurus japonicas group was improved when compared with the oxytocin group ($P<0.01$). There were no significant differences concerning TT levels before and after operation between the two groups (both $P>0.05$); compared with the oxytocin group, postpartum FIB level in the leonurus japonicas group was increased, while postpartum D-D and APTT levels were reduced (all $P<0.01$). The protein expression of ROCK I and ROCK II in the leonurus japonicas group before and after operation were higher than those in the oxytocin group (both $P<0.01$). Total effective rate of prevention in the leonurus japonicas group was increased when compared with the oxytocin group ($P<0.05$). Total incidence of adverse reactions in the leonurus japonicas group was slightly lower than that in the oxytocin group ($P>0.05$). Conclusion: Leonurus japonicus injection may be effective in preventing postpartum hemorrhage after cesarean section, improving the protein expression of ROCK I and ROCK II, and promoting uterine contractility, resulting in an ideal preventive effect.

Keywords: Leonurus japonicus injection, cesarean section, postpartum hemorrhage, ROCK

Introduction

Postpartum hemorrhaging can be alarming to parturients and threatens their life and safety. It is a common complication in obstetrics and gynecology. Massive postpartum hemorrhaging is the main cause of maternal death. When the volume of postpartum hemorrhage is more than 500 mL, parturients are at a high safety risk. Therefore, it is very important to quickly and effectively find a way to prevent postpartum hemorrhage after cesarean section [1]. Oxytocin is commonly applied in clinical practice to prevent postpartum hemorrhaging after cesarean section. It is a peptide hormone that can promote uterine smooth muscle contraction. This means that oxytocin can stimulate uterine smooth muscle and increase the sensitivity of oxytocin receptors, which are present in uterine smooth muscle, to ultimately, help prevent postpartum hemorrhaging. However, the situation of each parturient is unique. In other words, the density of oxytocin receptors present in uterine smooth muscle is different in

each individual. As a result, parturients' sensitivity to oxytocin is not consistent, and oxytocin's effect on preventing postpartum hemorrhaging varies [2]. Leonurus japonicus injection is one of the classical traditional Chinese medicines applied in regulating menstruation and the contracting uterus. Regulation of menstruation, removal of toxic substances, promotion of blood circulation, and elimination of blood stasis are the functions of leonurus japonicus. It is mainly used to treat irregular menstruation, detention of placenta, abdominalgia with blood stasis, and metrorrhagia. Leonurus japonicus injection can effectively increase the excitability of uterine smooth muscle, raise the frequency of contraction, enhance uterine contractility, and inhibit platelet aggregation and thrombosis, effectively preventing the occurrence of postpartum hemorrhaging [3]. In this study, we investigated the effect of leonurus japonicus injection on preventing postpartum hemorrhage after cesarean section and its influence on the protein expression of Rho-associated kinase (ROCK) I and ROCK II.

Materials and methods

General information

In total, 106 parturients admitted to Ningbo Zhenhai People's Hospital for caesarean section between April 2017 and April 2018 were recruited in this study. According to a random number table, parturients were allocated to the oxytocin group and the leonurus japonicus group (53 patients for each group). In the oxytocin group, parturients were 21-36 years old, and the average age was 28.5±6.0 years old; weeks of gestation were 36-41 weeks, and the average gestational age was 38.5±2.0 weeks; there were 24 primiparas and 29 postpartum women; as for pregnancy type, 45 parturients were with singleton pregnancy, 8 parturients were with twin pregnancy; 12 parturients had a history of cesarean section; and 8 parturients had uterine fibroids. In the leonurus japonicus group, parturients were 22-38 years old, and the average age was 30.0±6.4 years old; weeks of gestation were 37-41 weeks, and the average gestational age was 39.0±1.6 weeks; there were 28 primiparas and 25 postpartum women; as for pregnancy type, 47 parturients were with singleton pregnancy, 6 parturients were with twin pregnancy; 13 parturients had a history of cesarean section; and 7 parturients had uterine fibroids. There were no significant differences concerning the above data between the two groups (P>0.05).

Informed consent was signed by the patients or their family members. This study was approved by the Ethics Committee of Ningbo Zhenhai People's Hospital.

Inclusion criteria: Parturients showed normal fetal development; parturients had high-risk factors for uterine atony, and indications for cesarean section; parturients had pregnancy complications such as pregnancy-induced hypertension and gestational diabetes.

Exclusion criteria: Parturients were allergic to drugs used in this study; parturients with blood system disorders, like blood coagulation dysfunction; parturients with malformations of the reproductive tract; parturients had heart, liver, kidney or other important organ dysfunction; parturients with malignant tumors; parturients had autoimmune diseases; parturients with oligohydramnios, macrosomia, fetal distress; or parturients had cervical laceration.

Oxytocin was bought from Shanghai Hefeng Pharmaceutical Co., Ltd., China (10 units/mL). Leonurus japonicus injection was purchased from Chengdu First Pharmaceutical Co., Ltd., China (1 mL*2 sticks/box).

Methods

Interventions: Parturients in the oxytocin group were injected with oxytocin. After the fetus was born, the umbilical cord was clamped with blood vessel forceps, and 10 U of oxytocin was injected into the maternal uterine muscle wall. Oxytocin dissolved in 500 mL of 5% glucose solution was intravenously injected at 2 h post-surgery, and 10 U of oxytocin was injected within 12 h. The injections lasted for 3 days. In the leonurus japonicus group, parturients were injected with leonurus japonicus. Leonurus japonicus (2 mL) was intramuscularly injected at 2 h post-surgery. Similarly, the injections lasted for 3 days.

Blood loss: Sterile gauze was used to soak up the blood collected in a curved plate. The weight and volume were applied to evaluate blood loss at 12 hours and 24 hours after oper-

ation. Blood loss = weight change of sterile gauze before and after collection/1.05.

Postpartum uterine contractility: The JZJ01A muscle tension converter and BL420E biological function system were used to record the 24 h postpartum uterine contraction curve of parturients in both groups. Uterine contractility like amplitude, frequency, intensity and tension were analyzed.

Coagulation function: Fasting venous blood (6 ml) of parturients in both groups before and 4 d after operation were collected, and were placed into a non-heparin and heparin anticoagulation tube (3 mL in each tube). After centrifuging at 2,500 r/min for 10 min, plasma and serum were separated. A full-automatic coagulation analyzer (BS-490, Mindray, Wuhan Jiahang Medical Investment Management Co., Ltd., China) was applied to detect fibrinogen (FIB), D-dimer (D-D), activation part thrombin time (APTT), and thrombin time (TT).

Protein expression of ROCK I and ROCK II: Western blot was used to measure the protein expression of ROCK I and ROCK II of parturients in both groups before and 4 d after cesarean section. Fasting venous blood was collected early in the morning. Ficoll-Hypaque density gradient centrifugation method was applied to separate peripheral venous blood mononuclear cells. Protein from mononuclear cells was extracted and quantitatively measured using bicinchoninic acid (BCA) method. Protein (50 μg) was loaded to conduct SDS-PAGE electrophoresis. Thereafter, these proteins were transferred to a polyvinylidene fluoride membrane, which was blocked for 1 h in the dark. After washing, the primary antibody solution of ROCK I (Shenzhen Haodi Huatuo Biological Technology Co., Ltd., China, product number: P251535, dilution: 1:1,000) and ROCK II (Shenzhen Haodi Huatuo Biological Technology Co., Ltd, China, product number: 251573, dilution: 1:1,000) were respectively added and incubated overnight at 4C. After washing, the secondary antibody solutions, which were diluted 1:5,000, were added and incubated at 37C for 1 h. After washing, luminescent solution electrochemiluminescence (ECL) was added. Proteins were exposed three times, and the overlap value was recorded. The gray value of protein bands was calculated with GAPDH as the internal reference protein.

Preventive effect: According to the postpartum uterine contractility and blood loss at 24 h after operation, preventive effect was divided into three grades: markedly effective, effective, and ineffective. Markedly effective: postoperative uterine contractility was obvious, and blood loss at 24 h after operation was less than 100 mL. Effective: postpartum uterine contractility was observed, and blood loss at 24 h after operation was between 100 and 200 mL. Ineffective: Postpartum uterine contractility was not obvious or observed, and blood loss at 24 h after operation was more than 200 mL. Total effective rate = (markedly effective + effective)/the total number of patients * 100%.

Adverse reactions: Adverse reactions such as dyspnea and chest discomfort, increased blood pressure, and flushing were recorded.

Statistical methods

All data were analyzed using SPSS statistical software version 20.0. The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd). Independent sample t-test was used for inter-group comparison, while paired t-test was applied for before-after comparison within the same group. The enumeration data were expressed as number/percentage (n/%); comparison was conducted with chi-square test. The difference was statistically significant when *P* value was less than 0.05.

Results

Baseline data

As displayed in **Table 1**, there were no significant differences concerning baseline data such as average age, average gestational week, parity, pregnancy type, the history of cesarean section, and presence or absence of uterine fibroids between the two groups (all P>0.05).

Blood loss

Blood loss in the leonurus japonicus group at 12 h and 24 h after operation were less than those in the oxytocin group (**Table 2**, both P<0.01).

Postpartum uterine contractility

As shown in **Table 3**, postpartum uterine contractility in the leonurus japonicus group was

Table 1. Baseline data ($\bar{x}$ ± sd)

Group	Oxytocin group (n=53)	Leonurus japonicus group (n=53)	t/χ^2	P
Average age (years)	28.5±6.0	30.0±6.4	1.245	0.216
Average gestational week (weeks)	38.5±2.0	39.0±1.6	1.137	0.258
Parity			0.604	0.437
Primiparas	24	28		
Postpartum	29	25		
Pregnancy type			0.329	0.566
Singleton pregnancy	45	47		
Twin pregnancy	8	6		
The history of cesarean section			0.052	0.819
Present	12	13		
Absent	41	40		
Uterine fibroids			0.078	0.781
Present	8	7		
Absent	45	46		

Table 2. Blood loss ($\bar{x}$ ± sd)

Group	Blood loss at 12 h after operation (mL)	Blood loss at 12 h after operation (mL)
Oxytocin group (n=53)	245.39±25.38	465.21±80.78
Leonurus japonicus group (n=53)	135.26±13.46	286.30±53.16
t	27.910	13.470
P	0.001	0.001

improved when compared with that in the oxytocin group (P<0.01).

Coagulation function

As displayed in **Table 4**, there were no significant differences on prenatal FIB, D-D, APTT, and TT levels between the two groups (all P>0.05). There were no significant differences on prenatal and postnatal TT levels between the two groups (both P>0.05). Compared with prenatal FIB level, postnatal FIB level was decreased in both groups, while D-D and APTT levels were increased (P<0.01). Postpartum FIB level in the leonurus japonicus group was higher than that in the oxytocin group, while D-D and APTT levels were lower (all P<0.05).

Protein expression of ROCK I and ROCK II

As shown in **Table 5** and **Figure 1**, there were no significant differences concerning the protein expression of ROCK I and ROCK II between the two groups before operation (P>0.05). The protein expression of ROCK I and ROCK II in both groups after operation were higher than that before operation (both P<0.05). The protein expression of ROCK I and ROCK II in the leonurus japonicus group after operation was increased when compared with the oxytocin group (P< 0.01).

Prevention effect

Compared with the oxytocin group, total effective rate of prevention in the leonurus japonicus group was increased (**Table 6**, P<0.05).

Adverse reactions

As displayed in **Table 7**, total incidence of adverse reactions in the leonurus japonicus group was slightly lower than that in the oxytocin group (P>0.05).

Discussion

Postpartum hemorrhage is the main cause of maternal death. It is a high safety risk to cesarean sections. Placenta previa, polyhydramnios, and macrosomia are the high-risk factors weakening uterine contractility. The risk of postpartum hemorrhage after cesarean section is increased by these factors [4]. Finding effective drugs to prevent postpartum hemorrhaging after cesarean section is of great importance to the prognosis of parturients. Here, in order to prevent postpartum hemorrhaging we analyzed the effect of leonurus japonicus injection on preventing postpartum hemorrhage after cesarean section and its influence on the protein expression of ROCK I and ROCK II.

At present, hemostatic drug therapy is the main treatment used to prevent postpartum hemorrhaging. After being injected with the drug, parturients' uterine contractility is enhanced and the incidence of postpartum hemorrhaging is reduced [5]. In clinical practice, oxytocin is a

Table 3. Postpartum uterine contractility ($\bar{x}$ ± sd)

Group	Amplitude (mm)	Frequency (times/min)	Intensity (mm)	Tension (mm)
Oxytocin group (n=53)	246.39±25.16	0.75±0.26	1542.26±215.12	1432.25±213.05
Leonurus japonicus group (n=53)	452.23±45.25	0.32±0.12	1765.29±268.59	1596.38±235.46
t	28.940	10.930	4.718	3.763
P	0.001	0.001	0.001	0.001

Table 4. Coagulation function ($\bar{x}$ ± sd)

Group	Oxytocin group (n=53)	Leonurus japonicus group (n=53)	t	P
FIB (g/L)				
Prenatal	3.65±0.71	3.68±0.72	0.216	0.829
Postnatal	2.75±0.59	3.02±0.61	2.316	0.023
t	7.098	5.092		
P	0.001	0.001		
D-D (mg/L)				
Prenatal	0.71±0.18	0.72±0.19	0.278	0.781
Postnatal	0.99±0.18	0.84±0.15	4.661	0.001
t	8.008	3.609		
P	0.001	0.001		
APTT (s)				
Prenatal	28.65±2.15	28.63±2.13	0.048	0.962
Postnatal	39.46±3.15	35.26±2.13	8.041	0.001
t	20.640	16.020		
P	0.001	0.001		
TT (S)				
Prenatal	15.68±1.35	15.72±1.32	0.154	0.878
Postnatal	16.21±1.30	16.12±1.58	0.320	0.749
t	1.826	1.414		
P	0.071	0.160		

Note: FIB: fibrinogen; D-D: D-dimer; APTT: activation part thrombin time; TT: thrombin time.

Table 5. Protein expression of ROCK I and ROCK II ($\bar{x}$ ± sd)

Group	Oxytocin group (n=53)	Leonurus japonicus group (n=53)	t	P
ROCK I				
Prenatal	21.71±2.24	21.81±2.29	0.227	0.821
Postnatal	23.00±2.71	27.95±3.34	8.378	0.001
t	2.671	11.040		
P	0.009	0.001		
ROCK II				
Prenatal	17.46±3.14	16.54±3.64	1.393	0.167
Postnatal	18.65±2.84	22.46±3.75	5.896	0.001
t	2.046	8.247		
P	0.043	0.001		

Note: ROCK: Rho-associated kinase.

common drug used to prevent postpartum hemorrhage. Oxytocin, a peptide hormone, can promote uterine contractility through binding to oxytocin receptors, which are present in uterine smooth muscle [6]. Oxytocin is intravenously or intramuscularly injected, and it can stimulate uterine contractility as soon as reaching the blood circulation. Postpartum hemorrhaging is then reduced [7]. Oxytocin can be used to prevent postpartum hemorrhage. However, its half-life is relatively short and uterine contractility is rapidly decreased after terminating injection. As a result, the preventive effect is not good. In addition, if a high dose of oxytocin is injected in a short period of time, the preventive effect would be counterproductive, and a series of adverse reactions can be induced [8]. Leonurus japonicus injection is helpful in regulating menstruation, relieving pain, promoting blood circulation, and removing blood stasis. Moreover, it has a long half-life, and thus can promote uterine contractility over a long time [9, 10]. Stachydrine and leonurine are the essential components of leonurus japonicus. Stachydrine can promote uterine contractility without elevating blood pressure [11, 12]. To a certain extent, leonurus japonicus injection can promote endometrial repair and is conducive to the elimination of blood stasis. It has been widely applied in the treatment of diseases such as endometriosis, dysmenorrhea, and lochia. Moreover, a number of ideal effects are achieved [13, 14]. In our study, compared with the oxytocin group, uterine contractility and coagulation function in the leonurus japonicus group were improved, while

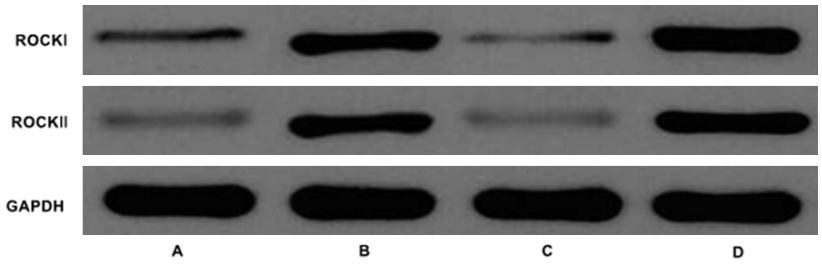

Figure 1. Protein expression of ROCK I and ROCK II in both groups before and after cesarean section. A: ROCK I and ROCK II proteins expressed in the oxytocin group before cesarean section; B: ROCK I and ROCK II proteins expressed in the oxytocin group after cesarean section; C: ROCK I and ROCK II proteins expressed in the leonurus japonicus group before; D: ROCK I and ROCK II proteins expressed in the leonurus japonicus group after cesarean section. ROCK: Rho-associated kinase.

Table 6. Preventive effect (%)

Group	Oxytocin group (n=53)	Leonurus japonicus group (n=53)	χ^2	P
Markedly effective	24 (45.28)	23 (43.40)	4.610	0.032
Effective	20 (37.74)	28 (52.83)		
Ineffective	9 (16.98)	2 (3.77)		
Total effective rate	44 (83.02)	51 (96.23)	4.970	0.026

Table 7. Adverse reactions (%)

Group	Dyspnea and chest discomfort	Increased blood pressure	Flushing	Total incidence of adverse reactions
Oxytocin group (n=53)	1 (1.89)	2 (3.77)	3 (5.66)	6 (11.32)
Leonurus japonicus group (n=53)	0	1 (1.89)	2 (3.77)	3 (5.66)
χ^2	1.010	0.343	0.210	1.093
P	0.315	0.558	0.647	0.296

postpartum hemorrhage was decreased. These results suggest that leonurus japonicus injection can enhance uterine contractility, improve coagulation function, and reduce postpartum hemorrhage.

ROCK protein, a serine/threonine protein kinase, has two isoforms (ROCK I and ROCK II) and is the downstream target of RhoA protein [15, 16]. RhoA protein can bind to ROCK once it is activated. Thereafter, the contractility of uterine smooth muscle is enhanced [17, 18]. Decreased protein expression of RhoA can influence the binding between RhoA and ROCK proteins, weakening the contractility of uterine smooth muscle and inducing the occurrence of postpartum hemorrhage [19]. The occurrence of postpartum hemorrhage is related to the RhoA protein, which is present in uterine smooth muscle tissue. When the protein expression of RhoA is decreased, the synthesis and secretion of peptide hormones are inhibited. Ultimately, the protein expression of ROCK I and ROCK II are reduced [20-22]. Leonurus japonicus injection can regulate the protein expression of ROCK I and ROCK II, so that synthesis and secretion of inhibin and activation peptide hormones are promoted, contractility of uterine smooth muscle is enhanced, and postpartum hemorrhage after cesarean section is prevented [23]. In our study, the protein expression of ROCK I and ROCK II in both groups after operation was significantly increased, and the change in the leonurus japonicus group was more than the oxytocin group.

In this study, we found that leonurus japonicus injection could promote uterine contractility and prevent postpartum hemorrhage through regulating the protein expression of ROCK I and ROCK II. However, we did not analyze the specific mechanism. In addition, the number of cases in our study is limited, and results may be not scientific. Therefore, subsequent studies will be carried out to verify our conclusions.

In summary, leonurus japonicus injection may be effective in preventing postpartum hemorrhaging after cesarean section, improving protein expression of ROCK I and ROCK II, and promoting uterine contractility, resulting in an ideal preventive effect.

Disclosure of conflict of interest

None.

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