Tropical Journal of Pharmaceutical Research November 2018; 17 (11): 2249-2254
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v17i11.20

Original Research Article

Anti-thrombotic effect of combination of low molecular heparin and Xueshuantong after replantation of amputated finger

Sun Huanwei, Yang Weidong, Zhang Hongquan, Wang Chunsheng, Zhong Yiming, Su Yi, Gao Bing, Sun Yang, Zou Xiaowei

Dalian Municipal Central Hospital Affliated of Dalian Medical University, Hand and Foot Surgery, Dalian, Liaoning 116033, China

For correspondence:* ***Email:* *uo1268@163.com*

Sent for review: 4 September 2018 *Revised accepted: 29 October 2018*

Abstract

Purpose: *To study the effects of low molecular heparin combined with Xueshuantong in preventing thrombosis after replantation of amputated finger.*
Methods: *The treatment group (38 patients) was given 4500 IU of low molecular heparin sodium i.h. (hypodermic injection), q.d.(once daily), with 200 mL of 150 mg Xueshuantong injection and 5 % glucose injection, i.v.d. (intravenous drip), b.i.d. (twice daily). The control group received low molecular heparin sodium at 4500 IU i.h., q.d. alone. Treatment was for 3 days. Thereafter, D-dimer, fibrinogen, hemoglobin, platelets, prothrombin time (PT) and blood coagulation of patients in the 2 groups before and after treatment were compared. Differences in vasospasm, vascular thrombosis, finger necrosis, therapeutic effects and adverse reactions in patients in the 2 groups after treatment were recorded.*
Results: *There were significant improvements in fibrinogen, platelet, PT levels, and blood coagulation time after treatment, with improvements better in the treatment group than in the control group ($p < 0.05$). Vasospasm cases (3) were lower in the treatment group than in the control group (8, $p < 0.05$), while vascular thrombosis and finger necrosis in both groups were comparable. Therapeutic effects and recovery were better in the treatment group than in the control group ($p < 0.05$).*
Conclusion: *Combined injection of Xueshuantong and low molecular heparin exerts antithrombotic effects after replantation of amputated finger, improves coagulation function, and reduces incidence of vasospasm. It has better therapeutic effects than low molecular heparin, and it seems safe.*

Keywords: *Xueshuantong, Low molecular heparin, Replantation, Amputated finger, Thrombosis*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Replantation of amputated finger is a category of restitution surgery with the goal of repairing vessels of the amputated finger, complete debriding, and focusing on bone, nerve, tendon and other tissues. The surgery is followed by multi-aspect comprehensive treatment. A successful surgery results in recovery of the finger function. Success in replantation is assessed by the ability to rebuild the vascular circulatory system [1-3]. The success rate is still

low, in spite of the improvements in microsurgical techniques and the development of several new technologies [4]. The high failure rate may be caused by post-surgery thrombosis [5].

Generally, within 8 to 19 h after replantation of amputated finger, finger vasospasm and embolism may occur due to various factors, thus severely affecting surgical effects and even causing failure of surgery [6]. Therefore, positive measures need to be adopted to cope with finger vasospasm and embolism. In the past, drugs such as papaverine hydrochloride and heparin sodium were used to prevent crisis in vessels, but these resulted in adverse reactions. Patients often had symptoms such as headache, abdominal distention and hemorrhage [7].

Low molecular heparin acts by preventing the procoagulant effect of coagulation factor Xa. It acts synergistically by stimulating vascular endothelial cells to release cellular activator and coagulation pathway inhibitors of tissue factors; it inhibits the neutralization of platelet IV factor without affecting the aggregation of platelets, and indirectly dissolves thrombi [8]. Characteristically, low molecular heparin has high bioavailability and long half-life period. In addition, it lowers the activities of thrombin and XII factor. Studies have shown that incidents of deep venous thrombosis of lower limbs in anticoagulant therapy group are lower than those in routine treatment group, suggesting that low molecular heparin treatment can mitigate deep venous thrombosis of lower limbs [9]. Low molecular heparin and *Xueshuantong* injection are common antithrombotic drugs used to prevent vascular thrombosis in clinics. However, their antithrombotic effects after replantation of amputated finger are poorly understood. This research was aimed to investigate the antithrombotic effects of injection of combination of low molecular heparin and *Xueshuantong* after replantation of amputated finger in a clinical setting.

EXPERIMENTAL

General data

Seventy-six patients with replantation of amputated finger admitted to Dalian Municipal Central Hospital Affliated of Dalian Medical University from January 2015 to July 2018 were involved in this study. The inclusion criteria were: (1) complete breakoff of monoplane of middle proximal parts of 2 to 4 fingers and single finger, and (2) absence of blood diseases, coagulation disorders or diseases that influence tissue recovery. The exclusion criteria were: incomplete break off, multiple fingers or multiple plane break off cases, and (2) patients with diabetes, hypertension and severe disorders of liver and kidney functions.

This research was approved by the Ethical Committee of Dalian Municipal Central Hospital Affiliated of Dalian Medical University, Hand and Foot Surgery, Dalian, Liaoning, China, (approval no. 20188187), and was executed according to the Declaration of Helsinki promulgated in 1964 as amended in 1996 [10]. A total of 76 cases were enrolled and randomly divided into two groups using random number method. There were 38 cases in the treatment group, consisting of 26 males and 12 females, with ages between 21 and 49 years (mean age = 36.19 ± 6.83 years). There were 38 patients in the control group, consisting of 24 males and 14 females, aged 22 to 53 years (mean age = 38.44 ± 6.02 years). Other baseline data of patients in the two groups are shown in Table 1. There was no significant difference in general data between 2 groups ($p > 0.05$).

Table 1: General baseline data for patients in the two groups (n, $\bar{m}$ean ± SD)

Feature		Treatment group (n=38)	Control group (n=38)	X^2/t	P-value
Amputated finger	Index finger	11	14	0.546	0.761
	Middle finger	15	13		
	Ring finger	12	11		
Amputation plane	Median joint	18	22	0.844	0.358
	Proximal joint	20	16		
Amputation injury quality	Incision	18	20	1.415	0.493
	oppression	11	13		
	Avulsion	9	5		
Mean ischemic time (h)		4.62 ± 1.37	4.66 ± 1.41	-0.13	0.901
Vascular anastomosis conditions	2∶ 3	24	21	0.490	0.484
	2∶ 4	14	17		
Mean surgical time (min)		112.41 ± 7.26	114.74 ± 6.99	-1.43	0.158

Treatment methods

Surgical method

Surgery in all patients was performed by two associate chief physicians with more than 10 years of experience. Blind methods were adopted during the operation. The patients were given brachial plexus nerve block; the wounds were washed routinely, and then disinfected and surgically draped. Debridement was performed under the microscope to eliminate hardness without vitality and vessels without vitality and elasticity. The finger bones of the amputated finger and broken ends were shortened by about 0.5cm and preserved in an incubator at 2 to 5 ^{o}C. Cross K-wire finger fixation was performed, and suture lines were used to repair arteries, veins and nerves. Finally, the skin was sutured. All operations strictly followed appropriate criteria.

Treatment methods after surgery

Patients in the two groups were given 4 g amoxil capsule, *p.o.*(orally)*, q.d*., and 100 mg feprazone tablets, *p.o., b.i.d*. for 3 consecutive days. Patients in the control group were given low molecular heparin sodium (France Sanofi Winthrop Industrie Company. No 20131122, specification: 0.4ml: 4000 IU/unit) at 4500 IU, *i.h., q.d.* for 3 consecutive days. In addition to low molecular weight heparin, patients in the treatment group received *Xueshuantong* injection (lyophilized, Guangxi Wuzhou Pharmaceutical Group Incorporated Company, specification: 100 mg/unit, no. 20130812) at a dose of 150 mg + 5 % glucose in a volume of 200 mL, *i.v.d., b.i.d.* during the same period.

Observation indices

Fasting venous blood was collected 24 h before and after treatment. Fibrinogen, D-dimer, hemoglobin, platelet, PT and coagulation time of patients were determined. In addition, vasospasm, vascular embolism and finger necrosis 72 h after treatment were assessed. Therapeutic effects in both groups were compared 3 months after replantation, while adverse reactions were recorded during treatment.

Evaluation criteria of therapeutic effects

The therapeutic effects were categorized into four grades.: *senior grade*, which referred to primary healing i.e. no vascular risk, infection and wound after surgery; *good grade*: no infection, primary wound healing with presence of slight circulation disorder after surgery, but near-normal skin temperature, color, tension and capillary filling of replantation; *medium grade*: presence of obvious circulation disorder requiring special treatment after surgery; and *poor grade*: failed surgery manifested in occurrence of vascular crisis requiring further surgical probe, or necrosis in replantation finger.

Statistical analysis

Measurement data are presented as mean ± standard deviation (SD), and statistically analyzed using Student's *t*-test and paired *t*-test. Enumeration data were compared using Chi square test, while ranked data were compared using rank sum test. Statistical significance criterion was α = 0. 05. The analysis was performed using SPSS (version 18.0, IBM, USA).

RESULTS

Coagulation function in patients before and after treatment

After treatment, the improvement in the treatment group was significantly higher than that in the control group (p < 0.05). These results are shown in Table 2.

Table 2: Changes in blood coagulation indexes of patients in the two groups before and after treatment

Treatment group	Treatment group (n = 38)		Control group (n = 38)	
	Before treatment	After treatment	Before treatment	After treatment
D-dimer (mg·L^{-1})	0. 36 ± 0. 07	0. 39 ± 0. 08	0. 34 ± 0. 05	0.36 ± 0. 06
Fibrinogen (g·L^{-1})	3.41 ± 0.71	2. 84 ± 0. 63^{ab}	3. 62 ± 1.03	3.16 ± 072^{a}
Hemoglobin (g·L^{-1})	92.68 ± 12.41	93.46 ± 11.97	94.46 ± 11.35	95.27 ± 12.66
Platelets (×10^{9}·L $^{-1}$)	244.31 ± 11.89	208.67±12.74^{ab}	248.72 ± 12.22	216.30±11.49^{a}
PT (s)	13.94 ± 2.62	19.82 ± 3.41^{ab}	13.71 ± 2.45	17.56 ± 2.95^{a}
Coagulation time (s)	15.83 ± 4.34	31.59 ± 5.49^{ab}	15.77 ± 3.96	26.90 ± 4.28^{a}

Values are mean ± SD (n =38); ^{a}p < 0. 05, compared with the control group after treatment, ^{b}p < 0. 05, compared with this group before treatment

Vasospasm in patients 72 h after treatment

There were 3 cases of vasospasm in the treatment group, which were significantly lower than 8 vasospasm cases in the control group ($p < 0.05$) (Table 3). There was no statistically significant difference in vascular embolism and finger necrosis between the treatment and the control groups ($p > 0.05$).

Therapeutic effects of replantation of amputated finger

The treatment group had better therapeutic effects than the control group ($p < 0.05$): good grade recovery in the treatment group was 92.11%, while that of the control group was 73.68 % (Table 4).

Adverse reactions to drugs

During treatment, 2 patients in the treatment group had skin mucosal ecchymosis, accounting for 5.26 % adverse reaction. In the control group, there were 2 cases of abdominal pain, 2 cases of skin mucosal ecchymosis, and 4 cases of epistaxis, resulting in 21.05 % adverse reaction in this group, which was significantly higher than that of the treatment group ($X^2 = 4.146$; $p < 0.05 = 0.042$).

DISCUSSION

Replantation of amputated finger is one of the common surgical operations in clinics. The surgeon often controls reset and subtract operations to eliminate elastic vessels, thus sustaining vascular function in the amputated finger. After replantation of the amputated finger, patients often experience vasospasm and embolism due to external stimulation, which may directly cause failure of surgery. Thus, effective prevention of vasospasm and embolism has become the hallmark successful replantation of amputated finger [11].

The main ingredient of *Xueshuantong* is *Panax notoginseng* saponins (PNS), a drug for *activating* blood and *resolving stasis*, and *soothing meridian* and *collaterals* in clinics. It can effectively inhibit aggregation of platelets and increase blood volume. Thus, it is clinically applied in the treatment of heart and cerebral vascular embolism, and venous obstruction of central retina [12]. *Xueshuantong* enhances blood flow to the limbs, and it can effectively reduce incidence of vascular crisis [13].

Low molecular weight heparin, a low molecular-volume heparin made by de-polymerization of normal heparin, has relatively strong Xa factor activity (about 8 times stronger than normal heparin). High-activity Xa factor inhibits the anti-thrombus and bleeding effects of drugs, and can effectively reduce the adverse reaction of bleeding [14]. Some researchers have reported that the use of low molecular weight heparin is associated with small individual differences, significant anticoagulation effects, efficient temperature control, and less adverse reactions post-application [15].

D-dimer is an important parameter that reflects the functioning of human fibrinolysis. Increases in D-dimer indicate high coagulation state, and the levels of fibrinogen, hemoglobin and platelets, which are important components of human blood, are positively correlated with coagulation function [16]. The normal value of PT is about 12 to 14 s. A significant increase in PT over normal value is an indication of high coagulation state.

Table 3: Cases of vasospasm in the two groups during treatment [n (%)]

Group	Vasospasm		Vascular embolism		Finger necrosis	
	Present	Absence	Present	Absence	Present	Absence
Treatment	3 (7.89) [a]	35(92.11)	2 (5.26)	36(94.74)	1 (2.63)	37(97.37)
Control	8 (21.05)	30(78.95)	5 (13.16)	33(86.84)	3 (7.89)	35(92.11)
X^2	2.657		1.459		1.102	
P	0.103		0.227		0.294	

[a] $p < 0.05$, compared with the control group

Table 4: Recovery grades after replantation of amputated finger in the patients {n (%)}

Group	Excellent	Good	Medium	Bad	Total good
Treatment (n=38)	28 (73.68)	7 (18.42)	2 (5.26)	1 (2.63)	92.11[a]
Control (n=38)	16 (42.11)	12 (31.58)	7 (18.42)	3 (7.89)	73.68
z/X^2	-2.854				4.547
P	0.004				0.033

[a] $P < 0.05$, compared with the control group

Blood coagulation time refers to the time taken for coagulation to occur after blood release from the vessels, and it is an important index that reflects whether the human coagulation function is normal or not [17-20].

The results of this study show the use of combination of low molecular weight heparin and *Xueshuantong* resulted in significant reduction in local plasma and vascular embolism in patients who underwent replantation of amputated finger, when compared to the use of low molecular heparin alone. This finding may be attributed to the ability of *Panax notoginseng* saponins to inhibit surface activity of platelets and platelet aggregation, thereby increasing vascular blood volume. In addition, there were only 3 cases of vasospasm in the treatment group, relative to 8 vasospasm cases in control, an indication that local blood circulation in the replanted fingers of the treatment group was better. Thus, the combination medication produced significant effects. The overall good recovery of surgical patients was 92.11 % in the treatment group, which strongly suggests that the combination medication showed obvious advantages in improving local blood circulation while reducing vascular crisis.

CONCLUSION

The results obtained in the current investigation indicate that injection of *Xueshuantong* in combination with low molecular heparin prevents thrombosis after replantation of amputated finger by significantly improving local blood circulation in patients. The combined treatment also significantly reduces incidence of vasospasm, prevents thrombus and promotes wound healing after replantation of amputated fingers. The therapeutic effects and safety associated with the combination treatment are better than those of low molecular heparin.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors, all authors read and approved the manuscript for publication. Sun Huanwei conceived and designed the study, Sun Huanwei, Yang Weidong, Zhang Hongquan, Wang Chunsheng, Zhong Yiming, Su Yi, Gao Bing, Sun Yang, Zou Xiaowei collected and analysed the data, Sun Huanwei wrote the manuscript.

REFERENCES

1. *Zhang FF. Analysis of clinical effects of microscopic intelligent incubator in reducing infection after replantation of amputated fingers. Med Inf 2016; 29(32): 193-194.*
2. *Li L, Dong L, Zhang Y, Wu R, Ma LL, Gong JZ. Clinical study of surgical perioperative blood transfusion and postoperative infection. Chin J Nosocomiol 2016; 26(12): 2805-2807.*
3. *Forlini M, Date P, Ferrari LM, Lorusso M, Lecce G, Verdina T, Neri G, Benatti C, Rossini P, Bratu A, et al. Comparative Analysis of Retinal Reattachment Surgery with or without Internal Limiting Membrane Peeling to Prevent Postoperative Macular Pucker. Retina 2018; 38(9): 1770-1776.*
4. *Yu H, Wei L, Liang B, Hou S, Wang J, Yang Y. Nonsurgical factors of digital replantation and survival rate: A metaanalysis. Indian J Orthop 2015; 49(3): 265-271*
5. *Efanov JI, Rizis D, Landes G, Bou-Merhi J, Harris PG, Danino MA. Impact of the number of veins repaired in short-term digital replantation survival rate. J Plast Reconstr Aesthet Surg 2016; 69(5): 640–645.*
6. *Chen HW, Sun LS, Li M, Zhao Y, Su XL. Etiological characteristics of postoperative infections in patients undergoing replantation of severed finger and changes of levels of serological markers. Chin J Nosocomiol 2017; 27(17): 3968-3971.*
7. *Zhen XC, Zhou MW, Fu HJ, Zhang X, Li Y, Si YL, Zhao X, Duan JJ, Zhao SY, et al. The influences of demanded exercises on blood circulation after replantation of amputated finger. Chin J Microsurg 2016; 39(1): 92-94.*
8. *Xi G, Lu Xiong. Value of lower molecular heparin calcification in preventing deep venous thrombus after varicosity of lower limbs. Chin J Gen Surg 2016; 25(12): 1806-1810.*
9. *Wang HL, Sun JY, Zhang T, Liu L, Yang ZY, Li X, Zhang YZ. Clinical study of low molecular weight heparin in preventing deep venous thrombosis after pelvic and acetabular fractures. Chin J Exp Surg 2016; 33(8): 2054-2056.*
10. *World Health Organization. Declaration of Helsinki. Br Med J 1996; 313(7070): 1448-1449.*
11. *Yang R, Chen YX. Evaluation of effects of local medication of anti-vascular spasm on artery crisis after replantation of amputated finger. Zhejiang Med J 2017; 39(17): 1483-1485.*
12. *Ma WX, Wang BP, Zhang Y, Ke BX. Clinical trial of Xueshuantong injection combined with aspirin in patients with recurrent acute cerebral infarction. Chin J Clin Pharmacol 2017; 33(6): 554-557.*

13. Kang MJ, Zhang YN, Zhang BC, Wen CM. Clinical trial of edaravone injection combined with Xueshuantong freeze-dried powder in the treatment of senile cerebral infarction. Chin J Clin Pharmacol 2016; 32(21): 1930-1933.
14. Tang Y, Wang K, Shi Z, Yang P, Dang X. A RCT study of Rivaroxaban, low-molecular-weight heparin, and sequential medication regimens for the prevention of venous thrombosis after internal fixation of hip fracture. Biomed Pharmacother 2017; 92: 982-988.
15. He XY, Chen LM, Liu PJ, Chen MZ, Wu DY. Meta-analysis for clinical effects of Shuxuetong and low-molecular-weight heparin in patients with deep vein thrombosis in lower limbs. Chin J Geriatr 2017; 36(10): 1130-1135.
16. Wu Hao, Wang YX, Li WC, Huang B, Guo YF, Liu YJ, Wang JL, Luo K. Significance of dynamic monitoring of D-dimer levels in predicting deep vein thrombosis after spinal nerve repair. CRTER 2016; 20(26): 3863-3869.
17. Li JY, Chen AB, Shi JH. The influences of warfarin on blood coagulation factor and blood coagulation time. Chin Med J 2017; 97(42): 3347-3349.
18. Dan Shen (Salvia miltiorrhiza) in Medicine. [homepage on the Internet]. Springer Link Inc.; c2017 [cited 2018 Oct 2]. Available from: https://link.springer.com/book/10.1007%2F978-94-017-9466-4.
19. Acupuncture Médecine Traditionnelle Chinoise & Accidents Vasculaires Cérébraux. [homepage on the Internet]. Centre de documentation du GERA 192 chemin des cèdres; c1970-2007 [cited 2018 Oct 2]. Available from: http://www.amcmh.org/PagAMC/downloads/avc-biblio.pdf.