Journal of Hainan Medical University

http://www.hnykdxxb.com

Effect of α−lipoic acid combined with nerve growth factor on bone metabolism, oxidative stress and nerve conduction function after femoral fracture surgery

An−Jun Cao✉, Jian−Hui Yang, Peng−Lin Mou, Jun Wang

Surgery Department No. 1, Guangzhou Xinhai Hospital, the Second Affiliated Hospital of Guangdong Pharmaceutical University in Guangdong Province, Guangzhou City, Guangdong Province, 510300

ARTICLE INFO

Article history:
Received 25 Oct 2017
Received in revised form 28 Oct 2017
Accepted 2 Nov 2017
Available online 14 Nov 2017

Keywords:
Femoral fracture
α-lipoic acid
Bone metabolism
Oxidative stress
Nerve conduction

ABSTRACT

Objective: To discuss the effect of α-lipoic acid combined with nerve growth factor on bone metabolism, oxidative stress and nerve conduction function after femoral fracture surgery. **Methods:** A total of 110 patients with femoral fracture who received surgical treatment in the hospital between January 2015 and January 2017 were collected and divided into the control group (n=55) and study group (n=55) by random number table. Control group received postoperative nerve growth factor therapy, and study group received postoperative α-lipoic acid combined with nerve growth factor therapy. The differences in the contents of bone metabolism and oxidative stress indexes as well as the levels of nerve conduction function indexes were compared between the two groups before and after treatment. **Results:** Before treatment, the differences in the contents of bone metabolism and oxidative stress indexes as well as the levels of nerve conduction function indexes were not statistically significant between the two groups. After treatment, serum bone metabolism indexes BGP and P Ⅰ NP contents of study group were higher than those of control group while CTX-Ⅰ and TRAP contents were lower than those of control group; serum oxidative stress indexes TAC, CAT and SOD contents of study group were higher than those of control group while MDA content was lower than that of control group; limb nerve conduction velocity SCV and MCV levels of study group were higher than those of control group. **Conclusion:** α-lipoic acid combined with nerve growth factor therapy after femoral fracture surgery can effectively balance osteoblast/osteoclast activity, reduce oxidative stress and improve limb nerve conduction velocity.

1. Introduction

Femoral fracture is mostly caused by trauma and violence or high-altitude falling. Severe swelling and deformity can occur in the affected limbs, and emergency operative reduction of fracture end should be performed in the early stage[1,2]. A great majority of patients with femoral fracture are complicated by the nerve injury, and how to furthest repair the damaged nerve not only depends on the intraoperative anatomical reduction of fracture end, but is also closely related to postoperative proper drug intervention. Nerve growth factor has been proven to be able to promote fracture healing, and it has been found in animal experiments that the mechanical strength of callus that is short of nerve fibers is significantly lower, so the early postoperative adjuvant nerve growth factor therapy has been used in a variety of clinical fractures[3,4]. α-lipoic acid is a kind of super antioxidant, it was successfully applied in the treatment of diabetic peripheral neuropathy[5,6], currently some scholars believe that it may also have some benefits for fracture patients with nerve injury, but few related practice research is done at present. In this study, α-lipoic acid and nerve growth factor were used together after femoral fracture surgery, and the effects of the treatment on bone metabolism, oxidative stress and nerve conduction was discussed.

✉Corresponding author: An-Jun Cao, Surgery Department No. 1, Guangzhou Xinhai Hospital, the Second Affiliated Hospital of Guangdong Pharmaceutical University in Guangdong Province, Guangzhou City, Guangdong Province, 510300.

Fund Project: Science and Technology Plan Projects of Guangdong Province No: 2012B031200146.

2. Information and methods

2.1 Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with femoral fracture by imaging examination and combined with nerve injury; (2) without fracture history; (3) cooperating with the operation and postoperative medication, and without midway data loss. Exclusion criteria: (1) with pathological fracture; (2) with application history of α-lipoic acid and nerve growth factor; (3) allergic to α-lipoic acid and nerve growth factor; (4) combined with diabetic peripheral neuropathy; (5) combined with systemic infectious diseases.

2.2 Case information

A total of 110 patients with femoral fracture who received surgical treatment in the hospital between January 2015 and January 2017 were collected, they were in accordance with the inclusion and exclusion criteria, and the patients themselves/family members signed informed consent. The enrolled patients were divided into the control group (n=55) and study group (n=55) by random number table. Control group included 30 male cases and 25 female cases that were 51-78 years; study group included 29 male cases and 26 female cases that were 50-75 years old. Baseline data of the two groups were similar, and the study was discussed and approved by the hospital ethics committee.

2.3 Therapy

Both groups of patients received normal femoral fracture surgery, and control group also received postoperative adjuvant nerve growth factor therapy, specifically as follows: intramuscular injection of 200 ng/kg nerve growth factor from the 1d after operation, 1 time/d, for 2 weeks. Study group received postoperative α-lipoic acid combined with nerve growth factor therapy as followings: oral administration of α-lipoic acid tablet from the 1 d after operation, 2 tablets (0.6 g)/time, 1 time/d, for 2 weeks.

2.4 Observation indexes

Before and after treatment, fasting cubital venous blood serum was obtained from two groups of patients, anti-coagulated and cryopreserved. Enzyme-linked immunosorbent assay was used to determine the serum levels of bone metabolism and oxidative stress indexes, bone metabolism indexes included osteocalcin (BGP), N-terminal propeptide of procollagen type I (PINP), cross-linked C-terminal telopeptides of type I collagen (CTX-I) and tartrate resistant acid phosphatase (TRAP); oxidative stress indexes included total antioxidant capacity (TAC), catalase (CAT), malondialdehyde (MDA) and superoxide dismutase (SOD). Electric neurodiagnostic instrument was used to measure the nerve conduction velocity of the affected lower limb, including sensory conduction velocity (SCV) and motor conduction velocity (MCV).

2.5 Statistical methods

Data input and calculation were both by software SPSS 25.0, and $P<0.05$ was the standard of statistical significance in differences in statistic. Bone metabolism, oxidative stress and nerve conduction function indexes all belonged to measurement data, were in terms of mean ± standard deviation and were compared by t test.

3. Results

3.1 Bone metabolism indexes

Comparison of serum bone metabolism indexes BGP (ng/mL), PⅠNP (pg/mL), CTX-Ⅰ (μg/mL) and TRAP (ng/mL) contents between the two groups was as follows: before treatment, serum BGP, PⅠNP, CTX-Ⅰ and TRAP contents were not significantly different between the two groups ($P>0.05$). After treatment, serum BGP and PⅠNP contents of both groups were higher than those before treatment whereas CTX-Ⅰ and TRAP contents were lower than those before treatment; serum BGP and PⅠNP contents of study group were higher than those of control group whereas CTX-Ⅰ and TRAP contents were lower than those of control group

Table 1.

Comparison of serum bone metabolism index contents.

Groups	n	BGP		PⅠNP		CTX-Ⅰ		TRAP	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	55	11.27±1.95	13.65±1.48*	9.27±1.05	11.53±1.86*	48.23±5.18	41.65±4.37*	29.62±3.45	22.77±2.85*
Study group	55	11.40±1.86	17.17±2.05*	9.41±1.13	14.78±1.97*	48.51±5.09	32.74±3.88*	29.58±3.29	17.53±2.19*
t		0.182	8.143	0.253	7.283	0.174	10.283	0.209	14.272
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

Table 2.

Comparison of serum oxidative stress index contents.

Groups	*n*	TAC (kU/L)		CAT (nU/mL)		MDA (μmol/L)		SOD (nU/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	55	10.27±1.68	12.85±1.74*	32.81±4.56	37.69±4.17*	4.72±0.58	3.86±0.41*	64.28±7.19	72.66±8.51*
Study group	55	10.31±1.59	15.79±1.88*	33.01±3.97	42.85±4.79*	4.69±0.56	3.17±0.34*	64.63±7.05	81.75±8.64*
t		0.182	7.293	0.261	12.483	0.214	6.271	0.179	10.928
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

($P<0.05$), shown in Table 1.

3.2 Oxidative stress indexes

Comparison of serum oxidative stress indexes TAC (kU/L), CAT (nU/mL), MDA (μmol/L) and SOD (nU/mL) contents between the two groups was as follows: before treatment, serum TAC, CAT, MDA and SOD contents were not significantly different between the two groups ($P>0.05$). After treatment, serum TAC, CAT and SOD contents of both groups were higher than those before treatment whereas MDA contents were lower than those before treatment; serum TAC, CAT and SOD contents of study group were higher than those of control group whereas MDA content was lower than that of control group ($P<0.05$), shown in Table 2.

3.3 Lower limb nerve conduction

Comparison of affected lower limb nerve conduction indexes SCV and MCV levels between the two groups was as follows: before treatment, affected limb SCV and MCV levels were not significantly different between the two groups ($P>0.05$). After treatment, affected limb SCV and MCV levels of both groups were higher than those before treatment; affected limb SCV and MCV levels of study group were higher than those of control group ($P<0.05$), shown in Table 3.

Table 3.

Comparison of low limb nerve conduction index levels (m/s).

Groups	*n*	SCV		MCV	
		Before treatment	After treatment	Before treatment	After treatment
Control group	55	32.18±4.27	37.66±4.05*	35.96±4.15	41.75±5.88*
Study group	55	32.09±4.16	43.87±4.92*	35.75±4.09	49.86±5.72*
t		0.218	9.283	0.175	8.265
P		>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

4. Discussion

The degree of limb function rehabilitation in patients with femoral fracture directly concerns the patient's long-term quality of life and subjective well-being, and current researches have pointed out that the affected limb function rehabilitation is not ideal in some patients with femoral fractures complicated by nerve injury, which can be directly related to the influence of nerve injury on fracture healing, body movement and sensory function, etc[7-9]. The treatment of patients with fracture complicated by nerve injury is more difficult than that of patients with fractures alone. How to furthest optimize the treatment outcome of such patients is the focus of current clinical research. Nerve growth factor is the common drug that promotes fracture healing, and the nerve growth factor receptor mRNA was highly expressed in the callus of rats with fractures, so the exogenous nerve growth factor can promote bone callus formation and fracture healing[10]. At the same time of accelerating fracture healing, how to restore the damaged nerve function is the key affecting the quality of the final fracture rehabilitation, α-lipoic acid, as a potent antioxidant, has been proven to be able to optimize the neural function in patients with diabetic peripheral neuropathy, and it is found that the osteoblast activity increases join in ovariectomized rats models after α-lipoic acid therapy, so it is considered to another reliable drug to optimize damaged fracture end nerves and promote fracture healing.

In this study, α-lipoic acid and nerve growth factor were used together after femoral fracture surgery, and the effect of the treatment on the progress of fracture healing was discussed at first. Fracture healing depends on bone formation cell/bone resorption cell function coordination. If bone resorption ability exceeds bone formation ability, bone mineralization obstacle and fracture healing delay will occur. Both BGP and PⅠNP are osteoblast function markers, BGP is secreted by osteoblasts and accumulates after bone mineralization peak, and its serum content is relatively stable and not affected by bone resorption[11]; PⅠNP is the only collagen in bone tissue and accounts for more than 90% of bone matrix, and its content intuitively reflects the osteoblast activity[12]. Both CTX-Ⅰ and TRAP are secreted by the osteoclasts, and research has confirmed that its level rises sharply in serum of patients with osteoporosis and is negatively correlated with bone mineral density value [13]. It was found in the study that compared with those before treatment, serum BGP and PⅠNP levels of both groups increased while CTX-Ⅰ and TRAP levels decreased after treatment; compared with those of control group, serum BGP and PⅠNP contents of study group were higher whereas CTX-Ⅰ and TRAP contents were lower after treatment, illustrating the α-lipoic acid combined with nerve growth factor after femoral fracture surgery can effectively optimize the bone formation/bone resorption balance of fracture end and promote the fracture healing.

The body is in an intense stress state after fracture occurs, a large number of oxygen free radicals are formed, further consume the contents of antioxidants and prompt lipid peroxidation formation, and oxidation product synthesis damages the fracture end tissue, blood vessels and nerve function, and hinders fracture healing and affected limb function recovery[14,15]. TAC, CAT and SOD are all factors that have antioxidant effect, which can neutralize excessive oxidative metabolites such as MDA and obstruct the lipid peroxidation process[16]. It was found in this study that compared with those before treatment, serum TAC, CAT and SOD levels of both groups increased whereas MDA levels decreased after treatment; further compared with those of control group, serum TAC, CAT and SOD contents of study group were higher whereas MDA content was lower after treatment, indicating that postoperative α-lipoic acid combined with nerve growth factor can effectively inhibit the systemic oxidative stress state in patients with femoral fractures, and this is also the one of the important mechanisms for it to promote fracture healing.

One of the most important measures for the treatment of femoral fracture patients with nerve injury is the nerve conduction function of the affected limb. The operation can repair the injured nerve to a certain extent, but the recovery degree of specific nerve function is directly related to the postoperative medication. Similar to those with diabetic peripheral nerve injury, patients with femoral fracture complicated by nerve damage are also with the reduction of affected limb nerve sensory and motor conduction velocity, and the specific reduction extent is highly consistent with nerve injury severity. In this study, it was found that compared with those before treatment, the SCV and MCV levels of both groups increased after treatment; further compared with those of control group, SCV and MCV levels of study group were higher after treatment, indicating that postoperative α-lipoic acid combined with nerve growth factor therapy can effectively improve the patient's damaged nerve function and help the full recovery of long-term limb function.

Early postoperative α-lipoic acid combined with nerve growth factor therapy can effectively optimize the bone metabolism, inhibit the systemic oxidative stress and strengthen the nerve conduction function in patients with femoral fractures complicated by nerve injury, it is expected to become the new way to improve the final treatment outcome of patients with such fractures, and it is worthy of popularization and application in clinical practice in the future.

References

[1] Giordano V, Godoy-Santos AL, Belangero WD, Pires RES, Labronici PJ, Koch HA. Finite element analysis of the equivalent stress distribution in Schanz screws during the use of a femoral fracture distractor. *Rev Bras Ortop* 2017; **52**(4): 396-401.

[2] Huang J, Pan J, Xu M, Xu S. Successful open reduction and internal fixation for displaced femoral fracture in a patient with osteopetrosis: Case report and lessons learned. *Medicine (Baltimore)* 2017; **96**(33): e7777.

[3] Fusco R, Gugliandolo E, Campolo M, Evangelista M, Di Paola R, Cuzzocrea S. Effect of a new formulation of micronized and ultramicronized N-palmitoylethanolamine in a tibia fracture mouse model of complex regional pain syndrome. *PLoS One* 2017; **12**(6): e0178553.

[4] Sang XG, Wang ZY, Cheng L, Liu YH, Li YG, Qin T, et al. Analysis of the mechanism by which nerve growth factor promotes callus formation in mice with tibial fracture. *Exp Ther Med* 2017; **13**(4): 1376-1380.

[5] Khalili M, Soltani M, Moghadam SA, Dehghan P, Azimi A, Abbaszadeh O. Effect of alpha-lipoic acid on asymmetric dimethylarginine and disability in multiple sclerosis patients: A randomized clinical trial. *Electron Physician* 2017; **9**(7): 4899-4905.

[6] Lee SJ, Jeong SJ, Lee YC, Lee YH, Lee JE, Kim CH, et al. Effects of high-dose α-lipoic acid on heart rate variability of type 2 diabetes mellitus patients with cardiac autonomic neuropathy in Korea. *Diabetes Metab J* 2017; **41**(4): 275-283.

[7] Saviola G, Prometti P, Ferrari PR, Dalle Carbonare LG. Atypical femoral fracture as first sign of non-hodgkin lymphoma- case report with a brief review of the literature. *Clin Ter* 2016; **167**(6): 188-190.

[8] Ghimire A, Bhattarai B, Koirala S, Subedi A. Analgesia before performing subarachnoid block in the sitting position in patients with proximal femoral fracture: a comparison between fascia iliaca block and femoral nerve block. *Kathmandu Univ Med J* 2015; **13**(50): 152-155.

[9] Chesters A, Atkinson P. Fascia iliaca block for pain relief from proximal femoral fracture in the emergency department: a review of the literature. *Emerg Med J* 2014; **31**(e1): e84-e87.

[10] Majuta LA, Longo G, Fealk MN, McCaffrey G, Mantyh PW. Orthopedic surgery and bone fracture pain are both significantly attenuated by sustained blockade of nerve growth factor. *Pain* 2015; **156**(1): 157-165.

[11] Suzuki Y, Maruyama-Nagao A, Sakuraba K, Kawai S. Level of serum undercarboxylated osteocalcin correlates with bone quality assessed by calcaneal quantitative ultrasound sonometry in young Japanese females. *Exp Ther Med* 2017; 13(5): 1937-1943.

[12] Vasikaran SD, Chubb SP, Ebeling PR, Jenkins N, Jones GR, Kotowicz MA, et al. Harmonised Australian Reference Intervals for Serum PINP and CTX in Adults. *Clin Biochem Rev* 2014; **35**(4): 237-242.

[13] Kodikara S, Kudagama M. Trap gun: an unusual firearm, aimed at wild animals but causing a silent epidemic of human fatalities. *Am J Forensic Med Pathol* 2014; **35**(1): 1-3.

[14] Li R, Fan L, Ma F, Cao Y, Gao J, Liu H, et al. Effect of etomidate on the oxidative stress response and levels of inflammatory factors from ischemia-reperfusion injury after tibial fracture surgery. *Exp Ther Med* 2017; **13**(3): 971-975.

[15] Li W, Liu Y, Wang B, Luo Y, Hu N, Chen D, et al. Protective effect of berberine against oxidative stress-induced apoptosis in rat bone marrow-derived mesenchymal stem cells. *Exp Ther Med* 2016; **12**(6): 4041-4048.

[16] Kanazawa I, Tomita T, Miyazaki S, Ozawa E, Yamamoto LA, Sugimoto T. Bazedoxifene ameliorates homocysteine-induced apoptosis and accumulation of advanced glycation end products by reducing oxidative stress in mc3t3-e1 cells. *Calcif Tissue Int* 2017; **100**(3): 286-297.