

doi: 10.13241/j.cnki.pmb.2017.21.036

α - 硫辛酸对 2 型糖尿病血管病变患者血清 CRP, IL-6, VEGF, VCAM-1 水平的影响 *

胡艳云¹ 李鸿燕² 边志颖¹ 贾丽艳¹ 陈 婕¹

(1 保定市第一中心医院东院 内分泌科 河北 保定 071000; 2 河北大学附属医院 内分泌科 河北 保定 071000)

摘要 目的:研究 α - 硫辛酸治疗 2 型糖尿病血管病变的临床疗效及其对血清 C 反应蛋白(CRP)、白细胞介素 -6(IL-6)、血管内皮生长因子(VEGF)、血管细胞黏附因子(VCAM-1)水平的影响。**方法:**选取 2015 年 8 月至 2016 年 7 月本院收治的 82 例 2 型糖尿病血管病变患者,根据随机数字法分为观察组和对照组,41 例每组。对照组使用甲钴胺治疗,观察组使用 α - 硫辛酸治疗。评价两组患者的临床疗效,比较两组患者治疗前后血清 CRP、IL-6、VEGF、VCAM-1 及血脂水平的变化。**结果:**治疗后,观察组总有效率显著高于对照组[92.68%(38/41)比 60.98%(25/41)]($P<0.05$)。治疗后,两组患者血清 CRP、IL-6、VEGF、VCAM-1、低密度脂蛋白胆固醇(LDL-C)、三酰甘油(TG)、总胆固醇(TC)水平较治疗前显著降低($P<0.05$),血清高密度脂蛋白胆固醇(HDL-C)水平较治疗前明显升高($P<0.05$)。与对照组相比,观察组治疗后血清 CRP、IL-6、VEGF、VCAM-1、LDL-C、TG、TC 水平更低($P<0.05$),HDL-C 水平较高($P<0.05$)。**结论:** α - 硫辛酸治疗能明显降低 2 型糖尿病血管病变患者血清 CRP、IL-6、VEGF、VCAM-1 水平,且临床疗效较好。

关键词: α - 硫辛酸; 2 型糖尿病; 血管病变; C 反应蛋白(CRP); 白细胞介素 -6(IL-6); 血管内皮生长因子(VEGF); 血管细胞黏附因子(VCAM-1)

中图分类号:R587.2 文献标识码:A 文章编号:1673-6273(2017)21-4143-04

Effect of α -lipoic Acid on Serum CRP, IL-6, VEGF and VCAM-1 Levels of Patients with Type 2 Diabetic Vascular Disease*

HU Yan-yun¹, LI Hong-yan², BIAN Zhi-ying¹, JIA Li-yan¹, CHEN Jie¹

(1 Third Department of Endocrinology, Baoding First Central Hospital, Baoding, Hebei, 071000, China;

2 Department of Endocrinology, Affiliated Hospital of Hebei University, Baoding, Hebei, 071000, China)

ABSTRACT Objective: To study the clinical effect of α -lipoic acid on the serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF) and vascular cell adhesion factor (VCAM-1) of patients with type 2 diabetes combined with vascular disease. **Methods:** 82 patients with type 2 diabetes mellitus who were treated in our hospital from August 2015 to July 2016 were selected and randomly divided into the observation group and the control group, with 41 patients in each group. The patients in the control group were treated with methylcobalamin, while the patients in the observation group were treated with α -lipoic acid. Then the serum levels of CRP, IL-6, VEGF, VCAM-1 and blood lipid in the two groups were observed and compared before and after the treatment. **Results:** After treatment, the total effective rate in the observation group was significantly higher than that of the control group ($P<0.05$). After treatment, the serum levels of CRP, IL-6, VEGF and VCAM-1 in the two groups were lower than those before treatment ($P<0.05$). Compared with the control group, the serum levels of CRP, IL-6, VEGF and VCAM-1 in the observation group were lower ($P<0.05$). After treatment, the serum levels of LDL-C, TG and TC in the two groups were significantly lower than those before treatment, while the HDL-C level was significantly higher ($P<0.05$). Compared with the control group, the serum levels of LDL-C, TG and TC in the observation group were lower, while the HDL-C was higher ($P<0.05$). **Conclusion:** α -lipoic acid could reduce the serum levels of CRP, IL-6, VEGF and VCAM-1 of patients with type 2 diabetes mellitus with obvious clinical curative effect.

Key words: α -lipoic acid; Type 2 diabetes; Vascular lesions; C reactive protein (CRP); Interleukin -6 (IL-6); Vascular endothelial growth factor (VEGF); Vascular cell adhesion factor (VCAM-1)

Chinese Library Classification(CLC): R587.2 **Document code:** A

Article ID: 1673-6273(2017)21-4143-04

前言

糖尿病主要是由胰岛素分泌缺陷或其生物学障碍所导致的以高血糖为特征的代谢性疾病,其并发症会给患者带来严重危害,尤其是糖尿病血管病变给患者生存质量带来严重影响,

也是患者面临致残或死亡的危险因素^[1,2]。糖尿病也被认为是低度炎症性疾病、天然免疫系统疾病及血管内皮功能紊乱而导致的血管性疾病^[3,4]。临床治疗 2 型糖尿病血管病变以药物治疗为主,目前临床中所使用的药物种类繁多,治疗效果有所不同^[5]。 α - 硫辛酸作为强效抗氧化剂,是治疗糖尿病血管病变的热门药

* 基金项目:河北省自然科学基金项目(C2009001061)

作者简介:胡艳云(1978-),女,本科,主治医师,研究方向:内分泌及其相关疾病,电话:13731271100

(收稿日期:2017-01-12 接受日期:2017-01-30)

物^⑨。为给临床治疗 2 型糖尿病血管病变提供更多可鉴之处,本研究探讨了 α - 硫辛酸治疗 2 型糖尿病血管病变的临床疗效及其对血清 C 反应蛋白(CRP)、白细胞介素 -6(IL-6)、血管内皮生长因子(VEGF)、血管细胞黏附因子(VCAM-1)水平的影响,报道如下。

1 资料与方法

1.1 临床资料

入选 2015 年 8 月至 2016 年 7 月在本院进行治疗的 82 例 2 型糖尿病血管病变患者,诊断标准^⑦:① 糖尿病神经病变;② 糖尿病肾病;③ 糖尿病视网膜病变;④ 糖尿病周围血管病变;⑤ 糖尿病合并脑血管病;⑥ 糖尿病合并冠心病。符合上述一项标准即可确定为糖尿病血管病变。纳入标准:① 和糖尿病血管病变诊断标准相符;② 患者自愿加入本次试验;③ 依从性较好者;④ 无用药禁忌症。排除标准:① 精神疾病史,意识不清晰者;② 当前正在进行其他项目研究;③ 临床资料缺失者;④ 酗酒史,化疗史及各种会对本次研究造成影响的诊疗史。整个研究均在患者及其家属的知情同意下完成,同时获得了本院伦理委员会的批准和实施。根据随机数字法分为观察组和对照组,41 例每组。其中观察组中男性 25 例,女性 16 例;年龄为 55~76 岁,平均(64.32 $\pm$ 3.03)岁;糖尿病病程为 2~7 年,平均(4.76 $\pm$ 0.54)年;糖尿病血管病变病程为 1~4 个月,平均(1.83 $\pm$ 0.23)个月;下肢动脉斑块形成或血管硬化狭窄者为 14 例,高血压合并者 8 例。对照组中男性 27 例,女性 14 例;年龄为 56~75 岁,平均(64.38 $\pm$ 3.08)岁;糖尿病病程为 2~6 年,平均(4.69 $\pm$ 0.51)年;糖尿病血管病变病程为 1~4 个月,平均(1.86 $\pm$ 0.25)个月;下肢动脉斑块形成或血管硬化狭窄者为 16 例,高血压合并者 9 例。

1.2 治疗方法

所有患者入院后需完成基础治疗,包括运动锻炼、饮食控制、血糖控制。对照组在基础治疗之上加以甲钴胺(生产厂家:

江苏四环生物制药有限公司,规格:0.5 mg/片,生产批号:20150211)完成治疗,0.5 mg/次,3 次/天。观察组在基础治疗之上加以 α - 硫辛酸(生产厂家:山东齐都药业有限公司,规格:12 s $\times$ 1 板,生产批号:20150215)0.2 g/次,3 次/天。所有患者在治疗期间,需每天测量空腹血糖。

1.3 观察指标

1.3.1 疗效评价 麻木感、冷感、或静息痛明显消失或减轻,和治疗前相比,间歇性跛行的行走距离增加程度 $\geq$ 2 倍则为显效;麻木感、冷感、或静息痛部分减轻,和治疗前相比,间歇性跛行的行走距离增加程度 1 倍则为有效;和治疗前相比,麻木感、冷感、或静息痛未发生变化则为无效;和治疗前相比,麻木感、冷感、或静息痛症状有所加重,间歇性跛行的行走距离明显缩短则为恶化^⑧。总有效 = 显效 + 有效。

1.3.2 血清 CRP、IL-6、VEGF、VCAM-1 及血脂水平分析 分别在治疗前后抽取两组患者 5 mL 的空腹静脉血,转速 3000 r/min,离心 15 min,分离血清后,提取上清液,放置在 -50℃ 低温箱中待测,使用酶联免疫双抗体夹心法测定 IL-6 水平,由法国国际免疫试剂公司提供 IL-6 酶联免疫药盒。使用 Quik Read CRP 分析仪检测 CRP 水平。血清脂代谢指标包括高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)、三酰甘油(TG)、总胆固醇(TC)。

1.4 统计学分析

本次实验数据处理选择 SPSS11.5 软件包进行,计量资料用($\bar{x} \pm s$)来表示,采用 t 检验,计数资料用[n(%)]来表示,采取 χ^2 检验,以 P<0.05 表明差异具有统计学意义。

2 结果

2.1 两组患者临床疗效比较

治疗后,观察组总有效率显著高于对照组[92.68%(38/41)比 60.98%(25/41)](P<0.05),见表 1。

表 1 两组患者临床疗效比较[n(%)]

Table 1 Comparison of the clinical effective between two groups[n(%)]

Groups	Cases	Markedly	Effective	Invalid	Deterioration	The total effective
Observation group	41	30(73.17)	8(19.51)	3(7.32)	0(0.00)	38(92.68)
Control group	41	10(24.39)	15(36.59)	11(26.83)	5(12.19)	25(60.98)

Note: Compared with control group, P<0.05.

2.2 两组患者治疗前后血清 CRP、IL-6、VEGF、VCAM-1 水平的比较

治疗前,两组患者血清 CRP、IL-6、VEGF、VCAM-1 水平比较差异均无统计学意义(P>0.05)。治疗后,两组患者血清 CRP、

IL-6、VEGF、VCAM-1 水平均较治疗前显著降低(P<0.05),且和对照组相比,观察组血清 CRP、IL-6、VEGF、VCAM-1 水平较低(P<0.05),见表 2。

表 2 两组患者治疗前后血清 CRP、IL-6、VEGF、VCAM-1 水平的比较($\bar{x} \pm s$)

Table 2 Comparison of the serum CRP, IL-6, VEGF, VCAM-1 levels before and after treatment between two groups($\bar{x} \pm s$)

Items	Observation group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
CRP(mg/L)	9.56 $\pm$ 0.98	5.64 $\pm$ 0.52 [*]	9.58 $\pm$ 0.95	7.39 $\pm$ 0.75 [*]
IL-6(mg/L)	121.43 $\pm$ 11.43	92.36 $\pm$ 9.21 [*]	121.49 $\pm$ 11.51	112.03 $\pm$ 10.02 [*]
VEGF(ng/L)	312.26 $\pm$ 31.21	84.32 $\pm$ 8.02 [*]	311.98 $\pm$ 31.17	134.54 $\pm$ 11.02 [*]
VCAM-1(U/L)	184.32 $\pm$ 18.21	131.23 $\pm$ 11.02 [*]	183.98 $\pm$ 18.18	167.54 $\pm$ 14.32 [*]

Note: Compared with before treatment, ^{*}P<0.05; Compared with control group after treatment, [#]P<0.05.

2.3 两组治疗前后血脂水平的比较

治疗前, 两组患者血清 HDL-C、LDL-C、TG、TC 水平比较差异均无统计学意义($P>0.05$); 治疗后, 两组患者血清 LDL-C、

TG、TC 水平均较治疗前显著降低($P<0.05$), HDL-C 水平明显升高($P<0.05$), 且与对照组相比, 观察组的血清 LDL-C、TG、TC 水平较低($P<0.05$), HDL-C 水平较高($P<0.05$), 见表 3。

表 3 两组治疗前后血脂水平的比较($\bar{x} \pm s$)

Table 3 Comparison of the blood lipid levels before and after treatment between two groups($\bar{x} \pm s$)

Items	Observation group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
HDL-C(mmol/L)	1.41± 0.21	1.98± 0.54	1.42± 0.22	1.63± 0.43
LDL-C(mmol/L)	3.32± 0.34	2.98± 0.23	3.35± 0.32	3.15± 0.28
TG(mmol/L)	2.25± 0.26	1.31± 0.14	2.27± 0.27	1.98± 0.19
TC(mmol/L)	5.87± 0.72	3.21± 0.25	5.84± 0.71	4.76± 0.46

Note: Compared with before treatment, * $P<0.05$; Compared with control group after treatment, # $P<0.05$.

3 讨论

血管病变是 2 型糖尿病慢性合并症的一种, 动脉粥样硬化是其病理基础。由于颈动脉位置的特殊性, 在获取各项参数时更加容易, 具有较好的重复性, 在临床中已将其作为评价全身动脉粥样硬化的理想方式, 并能对 2 型糖尿病患者的冠状动脉进行间接预测^[9,10]。在评价动脉粥样硬化中常常将血管内皮细胞功能障碍作为重要的标志, 在不同代谢路径作用下, 持续性高血糖产生活性氧, 对细胞内的氧化应激反应起着诱导性作用, 导致氧化应激产物出现, 对内皮细胞的相应分子受体产生作用, 进而发生血管收缩、血栓、炎症等病理改变^[11,12]。

甲钴胺作为内源性活性辅酶 B12 制剂中的一种, 具有扩张血管的作用, 对受损神经内膜的缺血缺氧状态发挥着明显的改善性作用, 降低缺血缺氧的受损程度, 对受损神经内膜发挥着保护性作用^[13,14]。 α -硫辛酸作为抗氧化剂中的一种, 能有效清除致病自由基, 对全身均可发挥作用, 被称之为万能抗氧化剂。由于 2 型糖尿病血管病变患者存在血管、神经等组织氧化损伤, 而 α -硫辛酸对高血糖损害能发挥明显的对抗作用, 提高机体细胞消耗糖类等能源物质的能力, 使血糖浓度处于平衡状态, 有利于全身症状的改善^[15,16]。本研究通过对 2 型糖尿病血管病变患者分别予以甲钴胺和 α -硫辛酸治疗后, 发现患者的血清 LDL-C、TG、TC 水平显著降低, HDL-C 水平明显升高, 提示患者的血脂水平均得到明显改善, 但经 α -硫辛酸治疗的患者血脂代谢指标改善的效果显著优于甲钴胺治疗者, 临床有效率也显著高于甲钴胺治疗者, 究其原因主要是因为 α -硫辛酸的抗氧化效果较为显著, 对氧化反应发挥着明显的逆转和阻断作用, 有利于患者微循环状况的改善, 进而提高治疗效果。

研究表明糖尿病微血管并发症糖尿病肾病的发生及发展均和 CRP、IL-6、VEGF、VCAM-1 有关。CRP 作为急性时相反应蛋白, 当各种损伤、急性炎症等疾病发作后, CRP 水平会在数小时内急剧升高, 伴随着患者病情的好转, CRP 水平又会降至正常范围^[17,18]。IL-6 能刺激骨髓造血干细胞、胸腺细胞、T 细胞增殖, 促进活化的 B 细胞分化, 对肝细胞发挥诱导作用, 产生急性期蛋白。糖尿病血管病变的发生很大程度上和慢性炎症诱导的 IL-6 生物合成增加有关, 并且疾病的严重程度和水平高低密切相关^[19]。VEGF 在血管内皮细胞中能发挥强有力的促分裂效应, 诱导血管内皮细胞增殖, 有利于新生血管形成。VEGF 在正常

血管组织中无表达, 而在动脉粥样硬化斑块中的表达会明显增加。VCAM-1 在高血脂、高血糖等作用下, 会对血管内皮产生刺激性作用, 破坏内皮的完整性, 增加 VCAM-1 的表达, 提升血管内皮细胞和白细胞之间的黏附力, 进而改变具备血液动力学环境, 导致微血管的嵌塞, 与此同时, 当周围组织受到白细胞侵袭后会有大量的炎性介质、细胞因子释放出, 损伤缺血区域组织, 也更有利于白细胞进入周围组织, 以此形成恶性循环状态^[20]。本研究结果显示 2 型糖尿病血管病变患者经 α -硫辛酸治疗后, 血清 CRP、IL-6、VEGF、VCAM-1 水平得到显著性降低, 降低效果优于甲钴胺治疗者, 提示 α -硫辛酸更能有效减轻 2 型糖尿病血管病变患者的炎症反应, 促进病情好转。

总之, α -硫辛酸治疗能明显降低 2 型糖尿病血管病变患者血清 CRP、IL-6、VEGF、VCAM-1 水平, 改善患者临床症状, 临床疗效良好。

参考文献(References)

- [1] Yang WM, Min KH, Lee W. Induction of miR-96 by Dietary Saturated Fatty Acids Exacerbates Hepatic Insulin Resistance through the Suppression of INSR and IRS-1[J]. PLoS One, 2016, 11(12): e0169039
- [2] Brewer RA, Gibbs VK, Smith DL Jr. Targeting glucose metabolism for healthy aging[J]. Nutr Healthy Aging, 2016, 4(1): 31-46
- [3] Famakin O, Fatoyinbo A, Ijarotimi OS, et al. Assessment of nutritional quality, glycaemic index, antidiabetic and sensory properties of plantain (Musa paradisiaca)-based functional dough meals[J]. J Food Sci Technol, 2016, 53(11): 3865-3875
- [4] Staszko M, Mieczkowski M. Management of diabetic kidney disease: a summary of European Recommendations 2015[J]. Wiad Lek, 2016, 69(5): 732-735
- [5] Fadaei R, Moradi N, Baratchian M, et al. Association of C1q/TNF-Related Protein-3 (CTRP3) and CTRP13 Serum Levels with Coronary Artery Disease in Subjects with and without Type 2 Diabetes Mellitus [J]. PLoS One, 2016, 11(12): e0168773
- [6] Uzu T, Araki SI, Kashiwagi A, Haneda M, et al. Comparative Effects of Direct Renin Inhibitor and Angiotensin Receptor Blocker on Albuminuria in Hypertensive Patients with Type 2 Diabetes. A Randomized Controlled Trial[J]. PLoS One, 2016, 11(12): e0164936
- [7] Hsu PC, Liao PY, Chang HH, et al. Nailfold capillary abnormalities are associated with type 2 diabetes progression and correlated with peripheral neuropathy[J]. Medicine (Baltimore), 2016, 95(52): e5714

- [8] Bailey CJ. Under-treatment of type 2 diabetes: Causes and outcomes of clinical inertia[J]. Int J Clin Pract, 2016, 70(12): 988-995
- [9] Abdelhafiz AH, Koay L, Sinclair AJ. The effect of frailty should be considered in the management plan of older people with Type 2 diabetes[J]. Future Sci OA, 2016, 2(1): FSO102
- [10] Shpakov AO, Derkach KV, Berstein LM. Brain signaling systems in the Type 2 diabetes and metabolic syndrome: promising target to treat and prevent these diseases[J]. Future Sci OA, 2015, 1(3): FSO25
- [11] Carter S, Clifton PM, Keogh JB. Intermittent energy restriction in type 2 diabetes: A short discussion of medication management [J]. World J Diabetes, 2016, 7(20): 627-630
- [12] Murillo Ortiz B, Ramírez Emiliano J, Ramos-Rodríguez E, et al. Brain-derived neurotrophic factor plasma levels and premature cognitive impairment/dementia in type 2 diabetes [J]. World J Diabetes, 2016, 7(20): 615-620
- [13] Li SD, Shi JH, Li XJ. Preventive effect of mecobalamin combined with glutathione on neurotoxicity induced by FOLFOX4 chemotherapy [J]. Chinese Journal of Oncology, 2016, 38(8): 632-635
- [14] Wang SA, Yang J, Zhang GB, et al. Effect of mecobalamin treatment on the recovery of patients with posterior communicating artery aneurysm inducing oculomotor nerve palsy after operation [J]. Eur Rev Med Pharmacol Sci, 2015, 19(14): 2603-2607
- [15] Veena RK, Ajith TA, Janardhanan KK, et al. Antitumor Effects of Palladium- α -Lipoic Acid Complex Formulation as an Adjunct in Radiotherapy[J]. J Environ Pathol Toxicol Oncol, 2016, 35(4): 333-342
- [16] Fiore E, Perillo L, Piccione G, et al. Effect of combined acetylmethionine, cyanocobalamin and α -lipoic acid on hepatic metabolism in high-yielding dairy cow[J]. J Dairy Res, 2016, 83(4): 438-441
- [17] Renner N, Wirth SH, Osterhoff G, et al. Outcome after protected full weightbearing treatment in an orthopedic device in diabetic neuropathic arthropathy (Charcot arthropathy): a comparison of unilaterally and bilaterally affected patients[J]. BMC Musculoskelet Disord, 2016, 17(1): 504
- [18] Shi X, Xue W, Liang S, et al. Acute caffeine ingestion reduces insulin sensitivity in healthy subjects: a systematic review and meta-analysis [J]. Nutr J, 2016, 15(1): 103
- [19] Lee HW, Jo AR, Yi DW, et al. Prevalent Rate of Nonalbuminuric Renal Insufficiency and Its Association with Cardiovascular Disease Event in Korean Type 2 Diabetes[J]. Endocrinol Metab (Seoul), 2016, 31(4): 577-585
- [20] Napora M, Grabowska E, Górska R. Prospective Analysis of the Relationship Between the State of Periodontal Tissues and Changes in Selected Cardiovascular Parameters in Patients with Type 2 Diabetes[J]. Adv Clin Exp Med, 2016, 25(5): 879-886

(上接第 4103 页)

- [14] Montaudie H, Seitz-Polski B, Comille A, et al. Interleukin 6 and high-sensitivity C-reactive protein are potential predictive markers of response to infliximab in hidradenitis suppurativa[J]. J Am Acad Dermatol, 2017, 76(1): 156-158
- [15] Pinski JK, Goldman B, Dorff T, et al. SWOG S0354: A phase II trial of CNT0328, a monoclonal antibody against interleukin-6 (IL-6), in chemotherapy pretreated patients (pts) with castration-resistant prostate cancer (CRPC)[J]. J Clin Oncol, 2009, 27(15): 5143
- [16] Fujiwara Y, Hizukuri Y, Yamashiro K, et al. Guanylate-binding protein 5 is a marker of interferon- γ -induced classically activated macrophages[J]. Clin Transl Immunology, 2016, 5(11): e111
- [17] Padilla-Quirarte HO, Trejo-Moreno C, Fierros-Zarate G, et al. Interferon-Tau has Antiproliferative effects, Represses the Expression of E6 and E7 Oncogenes, Induces Apoptosis in Cell Lines Transformed with HPV16 and Inhibits Tumor Growth *In Vivo*[J]. J Cancer, 2016, 7(15): 2231-2240
- [18] Douglas SD. Substance P and sickle cell disease-a marker for pain and novel therapeutic approaches [J]. Br J Haematol, 2016, 175(2): 187-188
- [19] He R, Yang L, Chen G, et al. Substance-P in symptomatic mediopatellar plica as a predictor of patellofemoral pain [J]. Biomed Rep, 2016, 4(1): 21-26
- [20] Faghih Z, Shobeiri SS, Ariafar A, et al. CD8⁺ T Lymphocyte Subsets in Bladder Tumor Draining Lymph Nodes [J]. Iran J Immunol, 2016, 13(4): 237-248
- [21] Ma Z, Bao X, Gu J. Effects of laparoscopic radical gastrectomy and the influence on immune function and inflammatory factors [J]. Exp Ther Med, 2016, 12(2): 983-986
- [22] Spahn DR, Spahn GH, Stein P. Indications and Risks of Fibrinogen in Surgery and Trauma[J]. Semin Thromb Hemost, 2016, 42(2): 147-154
- [23] Amin B, Zhang C, Yan W, et al. Effects of pneumoperitoneum of laparoscopic cholecystectomy on the coagulation system of patients: a prospective observational study[J]. Chin Med J (Engl), 2014, 127(14): 2599-2604