

doi: 10.13241/j.cnki.pmb.2019.14.031

不同剂量瑞舒伐他汀钙治疗脑梗死患者的临床疗效及机制研究*

张秋里 吴凤英[△] 王 宇 徐 彬 向宇鹏

(中国人民武装警察部队四川省总队医院神经内科 四川 乐山 614000)

摘要 目的:探讨不同剂量瑞舒伐他汀钙治疗脑梗死患者的临床疗效,并分析其疗效机制。**方法:**将2015年2月至2018年2月医院诊治的脑梗死患者84例按随机数字表法分为观察组(42例)及对照组(42例)。所有患者入院后均给予降血压、降血糖、稳定颅内压以及改善微循环等基本治疗,在此基础上,对照组口服瑞舒伐他汀钙10 mg/d,观察组口服瑞舒伐他汀钙20 mg/d,两组疗程均为14 d。比较两组疗效、治疗前后美国国立卫生研究所卒中量表(NIHSS)评分以及日常生活能力量表(Barthel指数)变化,并比较两组血清白细胞介素-6(IL-6)、白细胞介素-8(IL-8)、高迁移率族蛋白-1(HMGB1)和超敏C反应蛋白(hs-CRP)水平,分析血清HMGB1、IL-6、IL-8和hs-CRP之间的相关性,记录两组患者治疗过程中不良反应发生情况。**结果:**观察组治疗总有效率为95.24%(40/42),明显高于对照组的80.95%(34/42)($P<0.05$)。两组治疗后NIHSS评分均低于治疗前,Barthel指数高于治疗前,同时,观察组NIHSS评分降低程度大于对照组,Barthel指数升高程度大于对照组($P<0.05$)。治疗后两组患者血清IL-6、IL-8、HMGB1、hs-CRP明显降低,且观察组血清IL-6、IL-8、HMGB1、hs-CRP明显低于对照组($P<0.05$)。Person相关性分析表明患者血清HMGB1与IL-6、IL-8、hs-CRP呈正相关($r=0.306, 0.428, 0.367$, 均 $P<0.05$),IL-6与IL-8、hs-CRP呈正相关($r=0.327, 0.385, P<0.05$),IL-8与hs-CRP亦呈正相关($r=0.430, P<0.05$)。治疗期间两组不良反应发生率比较无统计学差异($P>0.05$)。**结论:**高剂量瑞舒伐他汀钙治疗脑梗死能够促进神经功能恢复,提高日常生活能力,临床疗效显著,其机制可能与降低脑梗死急性期炎症反应有关。

关键词: 脑梗死;瑞舒伐他汀钙;不同剂量;疗效;炎症因子;机制

中图分类号:R743 文献标识码:A 文章编号:1673-6273(2019)14-2747-04

Clinical Efficacy of Different Doses of Rosuvastatin Calcium in Treatment of Cerebral Infarction and Its Mechanism*

ZHANG Qiu-li, WU Feng-ying[△], WANG Yu, XU Bin, XIANG Yu-peng

(Department of Neurology, Sichuan Provincial Corps Hospital of Chinese Armed Police Force, Leshan, Sichuan, 614000, China)

ABSTRACT Objective: To investigate the clinical efficacy of different doses of rosuvastatin calcium in the treatment of cerebral infarction, and to analyze the mechanism of its efficacy. **Methods:** A total of 84 patients with cerebral infarction, who were treated in Sichuan Provincial Corps Hospital of Chinese Armed Police Force from February 2015 to February 2018, were randomly divided into observation group ($n=42$) and control group ($n=42$). All patients were given basic treatment, such as lowering blood pressure, lowering blood sugar, stabilizing intracranial pressure and improving microcirculation after admission. On the basis of the therapy, the control group was treated with rosuvastatin calcium with 10 mg/d, and the observation group was treated with rosuvastatin calcium with 20 mg/d, the course of treatment of two groups was 14 days. The therapeutic effect, changes in the National Institutes of Health Stroke Scale (NIHSS) and activity of daily living scale (Barthel Index) before and after treatment, the levels of serum interleukin-6 (IL-6), interleukin-8 (IL-8), high mobility group protein-1 (HMGB1) and hypersensitivity C reactive protein (hs-CRP) of the two groups were compared. The correlation among serum HMGB1 and IL-6, IL-8 and hs-CRP was analyzed. The occurrence of adverse reactions in the two groups was recorded. **Results:** The total effective rate [95.24% (40/42)] of the observation group was significantly higher than that [80.95% (34/42)] of the control group ($P<0.05$). After treatment, the NIHSS scores of the two groups were significantly decreased, the Barthel index was significantly increased, and the degree of reduction of the NIHSS score of the observation group was greater than that of the control group, the degree of increase of Barthel index in the observation group was greater than that of the control group ($P<0.05$). The levels of serum IL-6, IL-8, HMGB1, hs-CRP in the two groups were significantly decrease, the levels of serum IL-6, IL-8, HMGB1 and hs-CRP in the observation group were significantly lower than those in the control group ($P<0.05$). Person correlation analysis showed that serum HMGB1 was positively correlated with IL-6, IL-8, hs-CRP ($r=0.306, 0.428, 0.367, P<0.05$); IL-6 was positively correlated with IL-8 and hs-CRP ($r=0.327, 0.385, P<0.05$); there was also a positive correlation between IL-8 and hs-CRP ($r=0.430, P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups during treatment ($P>0.05$). **Conclusion:** In the treatment of

* 基金项目:四川省科技厅科研基金项目(2013ZF0268)

作者简介:张秋里(1982-),女,本科,主治医师,从事临床医学方面的研究,E-mail:lqegoo@163.com

[△] 通讯作者:吴凤英(1969-),女,本科,副主任医师,从事临床医学方面的研究,E-mail:yqwegn@163.com

(收稿日期:2018-11-24 接受日期:2018-12-18)

patients with cerebral infarction, high dose of rosuvastatin calcium can promote the recovery of nerve function and improve the daily living ability, with good clinical effect. Its mechanism may be related to the reduction of the acute inflammatory reaction in the cerebral infarction.

Key words: Cerebral infarction; Rosuvastatin calcium; Different doses; Efficacy; Inflammatory factors; Mechanism

Chinese Library Classification(CLC): R743 **Document code:** A

Article ID: 1673-6273(2019)14-2747-04

前言

脑梗死又称为缺血性卒中,是心脑血管的常见疾病,具有较高的发病率、致残率和致死率。有报道显示,目前我国脑梗死发病率高达 116~219/10 万,且发病率以每年 8.7% 的速度上升,给患者家庭和社会带来沉重负担^[1,2]。目前关于脑梗死的发病机制仍未完全明确,一般认为该病在动脉粥样硬化的基础上,粥样斑块破裂、血小板激活、血栓形成,进而引发相应的脑组织缺血坏死,而且炎症反应在整个过程中起到重要的作用^[3,4]。研究表明,他汀类药物除具有降脂作用外,还具有稳定动脉粥样硬化斑块的效果,对脑梗死有很好的疗效^[5-7],但何种剂量是临床治疗的最佳剂量尚且存在一定争议,同时,对其治疗机制也需要进一步明确^[8]。鉴于此,本研究通过探讨不同剂量瑞舒伐他汀钙治疗脑梗死患者的疗效及疗效机制,旨在为寻找瑞舒伐他汀钙治疗脑梗死的最佳剂量提供参考依据。

1 资料和方法

1.1 一般资料

将 2015 年 2 月至 2018 年 2 月于医院诊治的脑梗死患者 84 例作为研究对象。纳入标准:(1)符合全国第五届脑血管病学术会议纪要的诊断标准^[9];(2)经脑部 CT 或 MRI 确诊;(3)所有患者均签署了知情同意书。排除标准:(1)6 个月内有心肌梗死或接受过重大手术者;(2)肝、肾等脏器功能严重障碍者;(3)对药物过敏者;(4)合并急性炎症、肿瘤疾病者;(5)入院前接受过免疫抑制剂治疗者。根据随机数字表法分为对照组及观察组各 42 例。其中对照组男 24 例,女 18 例,年龄 34~81 岁,平均年龄(62.31±10.32)岁;疾病类型:腔隙性卒中 13 例,大动脉粥样硬化血栓形成 24 例,心源性卒中 5 例。观察组男 26 例,女 16 例,年龄 33~81 岁,平均年龄(62.62±10.93)岁;疾病类型:腔隙性卒中 12 例,大动脉粥样硬化血栓形成 23 例,心源性卒中 7 例。两组基线资料存在可比性($P>0.05$)。研究已得到院内伦理委员会批准。

1.2 研究方法

观察组、对照组患者入院后均行降血压、降血糖、颅内压及纠正微循环等常规治疗。同时在晚上 7 点 30 左右(餐后)温水口服瑞舒伐他汀钙片(浙江海正药业股份有限公司,国药准字:H20143338,10 mg×10 片/盒)治疗,其中对照组剂量为 10 mg/d,观察组剂量为 20 mg/d,以 14d 为 1 个疗程。

1.3 观察指标

1.3.1 神经功能以及日常生活能力 分别于治疗前、治疗 14 d 后应用美国国立卫生研究院卒中量表(National Institute of Health stroke scale,NIHSS)评分^[10]对患者神经功能进行评价,NIHSS 评分包括 11 项内容,总计 42 分,分数越低表明神经功能损伤越轻。采用日常生活能力量表(Barthel 指数)评估患者日

常生活能力^[11],Barthel 指数记分为 0~100 分,分数越高表明日常生活能力越强。

1.3.2 血清学指标检测 采集患者晨 8 点前空腹肘静脉血 5 mL(治疗前、治疗 14 d 后),经 4000 转/min 离心 10 min 后分离血清,应用酶联免疫吸附法测定患者血清白细胞介素-6(IL-6)、白细胞介素-8(IL-8)、高迁移率族蛋白-1(High mobility group box-1 protein,HMGB1)和超敏 C 反应蛋白(Hypersensitive C-reactive protein,hs-CRP)水平。IL-6、IL-8、hs-CRP 试剂盒购自武汉华美生物科技有限公司,HMGB1 试剂盒购自日本 Shino 公司,具体操作严格遵照说明书进行。

1.3.3 不良反应 观察两组治疗期间不良反应发生情况。

1.4 疗效评定

临床疗效主要根据 NIHSS 评分进行评估^[12]:(1)治愈:治疗后患者的 NIHSS 评分下降≥90%;(2)显效:治疗后患者的 NIHSS 评分下降 46%~89%;(3)有效:治疗后患者的 NIHSS 评分下降 18%~45%;(4)无效:治疗后患者的 NIHSS 评分下降低于 18%。总有效率=(治愈例数+显效例数+有效例数)/总例数×100%。

1.5 统计学方法

采用 SPSS 21.0 统计学软件对数据进行分析,计数资料以率(%)表示,组间比较以 χ^2 检验。计量资料以($\bar{x} \pm s$)表示,行 t 检验,应用 Person 相关分析方法分析血清 HMGB1、IL-6、IL-8、hs-CRP 之间的相关性, P 值<0.05 表明两组数据对比具有统计学意义。

2 结果

2.1 疗效对比

观察组治疗总有效率高于对照组($P<0.05$)。见表 1。

2.2 NIHSS 评分、Barthel 指数对比

治疗后两组 NIHSS 评分低于治疗前,Barthel 指数高于治疗前,且观察组 NIHSS 评分低于对照组,Barthel 指数高于对照组($P<0.05$)。见表 2。

2.3 两组不良反应发生情况比较

治疗期间观察组出现皮肤瘙痒 1 例、恶心呕吐 2 例、便秘 2 例,未出现肌无力、血清转氨酶升高,不良反应发生率为 11.90%(5/42);对照组出现皮肤瘙痒 2 例、恶心呕吐 3 例、便秘 1 例,不良反应发生率为 14.29%(6/42),两组不良反应发生率比较差异无统计学意义($\chi^2=0.080$, $P=0.777$)。

2.4 治疗前后两组血清炎症因子水平对比

治疗前两组血清 IL-6、IL-8、HMGB1、hs-CRP 比较无统计学差异($P>0.05$),治疗后两组患者血清 IL-6、IL-8、HMGB1、hs-CRP 均降低,且观察组以上指标均低于对照组($P<0.05$)。见表 3。

表 1 疗效对比 n(%)

Table 1 Comparison of the clinical efficacy [n(%)]

Groups	n	Cure	Excellence	Effective	Invalid	Total effective rate
Observation group	42	22(52.38)	13(30.95)	5(11.90)	2(4.76)	40(95.24)
Control group	42	18(42.86)	12(28.57)	4(9.52)	8(19.05)	34(80.95)
χ^2	-					4.086
<i>P</i>	-					0.043

表 2 NIHSS 评分和 Barthel 指数对比(分, $\bar{x} \pm s$)Table 2 Comparison of NIHSS score and Barthel index of two groups before and after treatment(score, $\bar{x} \pm s$)

Groups	n	NIHSS score		Barthel index	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	42	14.3 $\pm$ 3.3	5.4 $\pm$ 2.5*	38.6 $\pm$ 2.2	55.3 $\pm$ 3.1*
Control group	42	14.5 $\pm$ 3.4	7.8 $\pm$ 3.2*	38.8 $\pm$ 2.3	43.1 $\pm$ 2.9*
<i>t</i>	-	0.211	-2.812	0.407	2.825
<i>P</i>	-	0.834	0.000	0.685	0.000

表 3 治疗前后两组血清炎症因子水平对比($\bar{x} \pm s$)Table 3 Comparison of levels of serum inflammatory factors before and after treatment between two groups($\bar{x} \pm s$)

Groups	n	IL-6(μ g/L)		IL-8(pg/mL)		HMGB1(mg/L)		hs-CRP(mg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	42	12.7 $\pm$ 3.2	7.2 $\pm$ 2.4*	99.4 $\pm$ 24.3	67.3 $\pm$ 19.2*	12.3 $\pm$ 1.2	3.3 $\pm$ 0.8*	14.9 $\pm$ 3.2	5.3 $\pm$ 1.3*
Control group	42	12.8 $\pm$ 3.1	9.3 $\pm$ 3.0*	99.7 $\pm$ 23.9	81.5 $\pm$ 21.8*	12.1 $\pm$ 1.1	5.2 $\pm$ 1.0*	15.1 $\pm$ 3.1	7.7 $\pm$ 2.0*
<i>t</i>	-	0.145	2.742	0.057	2.968	0.291	2.708	0.482	2.712
<i>P</i>	-	0.885	0.001	0.955	0.000	0.772	0.012	0.630	0.008

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

2.5 血清 HMGB1、IL-6、IL-8 和 hs-CRP 之间相关性

Person 相关分析显示, 患者血清 HMGB1 与 IL-6、IL-8、hs-CRP 呈正相关($r=0.306, 0.428, 0.367$, 均 $P < 0.05$); IL-6 与 IL-8、hs-CRP 呈正相关($r=0.327, 0.385$, 均 $P < 0.05$), IL-8 与 hs-CRP 亦呈正相关($r=0.430, P < 0.05$)。

3 讨论

目前, 对于脑梗死尚无特异性疗法, 临床上主要是通过降血压、稳定颅内压、改善微循环、恢复脑组织血流供应、改善患者的神经功能缺损以及卒中后的炎症反应等进行治疗^[13-15]。以往临床上对于脑梗死更多关注的是恢复缺血区域的血流供应。近年来研究发现, 脑梗死的发生是在动脉粥样硬化病变基础上出现的脑组织缺血, 发病过程中除脑组织缺血性损伤外, 炎症反应和氧自由基损伤等也起到重要作用^[16-18]。而他汀类药物则可以通过稳定动脉粥样硬化斑块和降低病变部位炎症反应起到治疗效果。瑞舒伐他汀钙是一种新型水溶性降脂类药物, 它能够有效降低心血管事件发生率和死亡率^[19,20]。目前已有研究证实瑞舒伐他汀治疗心肌梗死、脑梗死效果良好^[21], 但关于其治疗合理剂量和药理机制的研究不多。

本研究, 观察组总有效率为 95.24%, 显著高于对照组的

80.95%。这与冯志霞等^[22]人的研究报道相似, 说明应用 20 mg/d 瑞舒伐他汀钙治疗脑梗死疗效更为显著, 其效果优于 10 mg/d。同时, 治疗后观察组和对对照组 NIHSS 评分、Barthel 指数分别降低和升高, 且观察组患者 NIHSS 评分降低幅度大于对照组, Barthel 指数升高程度亦大于对照组。这提示了 20 mg/d 剂量的瑞舒伐他汀钙治疗脑梗死有利于促进患者的神经功能恢复, 提高患者的日常生活能力。究其原因, 笔者认为这可能是与高剂量的瑞舒伐他汀钙药效相对较强有关。瑞舒伐他汀钙主要通过抑制甲基戊二酰辅酶 A 还原酶, 进而抑制内源性胆固醇的合成, 同时还可以通过刺激血管内皮细胞低密度脂蛋白受体的合成, 起到稳定血管内膜的作用^[23]。这种作用与瑞舒伐他汀钙的剂量有关, 因此应用 20 mg 临床疗效更佳。目前, 临床上对于瑞舒伐他汀钙的最佳应用剂量尚且存在一定争议, 其主要原因在于临床疗效和不良反应的综合决策。有报道显示, 大剂量的瑞舒伐他汀钙可能会增加患者发生不良反应的风险^[24,25]。本研究中两组不良反应发生率比较无统计学差异, 观察组未出现肌无力、血清转氨酶升高, 表明 20 mg 剂量在提高了临床疗效的同时并未增加患者的不良反应发生率。

目前, 对于瑞舒伐他汀钙疗效作用机制仍未明确。笔者通过研究发现治疗后两组患者血清 IL-6、IL-8、HMGB1、hs-CRP

显著降低,且观察组血清 IL-6、IL-8、HMGB1、hs-CRP 显著低于对照组。IL-6 是趋化因子家属的重要成员,同时也是一种多功能的促炎因子。研究表明 IL-6 可以促进炎症细胞的积聚和活化,从而刺激内皮细胞以及中性粒细胞等参与脑梗死的炎症反应过程^[26];IL-8 也是一种重要的促炎症因子,通过释放大量的炎症细胞介质,其可以促进中性粒细胞向病变部位聚集,参与脑梗死炎症反应过程^[27]。HMGB1 是一种 DNA 合成蛋白,也是一种新型的炎性因子,研究发现, HMGB1 能够通过活化炎症细胞,起到促进炎症反应的作用,是炎症反应的重要媒介^[28,29]。尤其是高血脂、高胆固醇可以促进 HMGB1 的活化,进一步引发炎症反应。hs-CRP 属非特异性炎症因子,可通过激活补体系统,进而使单核巨噬细胞中性粒细胞等移至血管内皮,从而形成血栓,直接参与了一些列炎症反应过程^[30]。本研究结果表明了瑞舒伐他汀钙治疗脑梗死的机制与改善患者血清炎性因子有关,从而起到更好的治疗效果。从 Person 相关分析来看,患者血清 HMGB1、IL-6、IL-8、hs-CRP 之间均呈正相关,提示在脑梗死发病中 HMGB1 可能与 IL-6、IL-8、hs-CRP 共同起到作用,而瑞舒伐他汀钙通过降低 HMGB1 与 IL-6、IL-8、hs-CRP 水平,以抑制炎症反应起到治疗作用。

综上所述,20 mg 瑞舒伐他汀钙治疗脑梗死能够促进神经功能恢复,提高日常生活能力,临床疗效显著,其机制可能与降低脑梗死急性期炎症反应有关。

参考文献(References)

- [1] Misumi I, Nagao A, Iwamoto K, et al. Acute Multiple Cerebral Infarction in a Patient with an Accessory Mitral Valve[J]. Intern Med, 2017, 56(2): 153-155
- [2] 邓立军,张淑琴,魏进,等.阿托伐他汀联合双抗血小板治疗对脑梗死患者疗效及对血清炎性因子水平的影响 [J]. 现代生物医学进展, 2017, 17(31): 6107-6110
- [3] Zaw KT, Sato N, Ikeda S, et al. Association of ZFHX3 gene variation with atrial fibrillation, cerebral infarction, and lung thromboembolism: An autopsy study[J]. J Cardiol, 2016, 5087(16): 30290-30298
- [4] Jabbarli R, Reinhard M, Niesen WD, et al. Predictors and impact of early cerebral infarction after aneurysmal subarachnoid hemorrhage [J]. Eur J Neurol, 2015, 22(6): 941-947
- [5] Ades S, Douce D, Holmes CE, et al. Effect of rosuvastatin on risk markers for venous thromboembolism in cancer [J]. J Thromb Haemost, 2018, 16(6): 1099-1106
- [6] Rodríguez-Perea AL, Gutierrez-Vargas J, Cardona-Gómez GP, et al. Atorvastatin Modulates Regulatory T Cells and Attenuates Cerebral Damage in a Model of Transient Middle Cerebral Artery Occlusion in Rats[J]. J Neuroimmune Pharmacol, 2017, 12(1): 152-162
- [7] Deguchi I, Horiuchi Y, Hayashi T, et al. Effects of rosuvastatin on serum lipids and arteriosclerosis in dyslipidemic patients with cerebral infarction[J]. J Stroke Cerebrovasc Dis, 2014, 23(8): 2007-2011
- [8] 李荣. 不同剂量瑞舒伐他汀钙对脑梗死患者 C 反应蛋白胆固醇低密度脂蛋白的影响[J].中国实用神经疾病杂志, 2016, 19(11): 99-100
- [9] 陈伟群,王新德.全国第五届脑血管病学术会议纪要[J].中华神经科杂志, 2000, 33(4): 59-61
- [10] Kim JT, Park MS, Choi KH, et al. Clinical Outcomes of Posterior Versus Anterior Circulation Infarction With Low National Institutes of Health Stroke Scale Scores[J]. Stroke, 2017, 48(1): 55-62
- [11] Park CS. The test-retest reliability and minimal detectable change of the short-form Barthel Index (5 items) and its associations with chronic stroke-specific impairments[J]. J Phys Ther Sci, 2018, 30(6): 835-839
- [12] 沈家萍,徐雯.脑梗死患者 NIHSS 评分与预后的相关性研究[J].中国社区医师, 2017, 33(10): 33-36
- [13] Nagahama H, Suzuki J, Sasaki M, et al. Evaluation of the Therapeutic Mechanisms in Regeneration Therapy for Cerebral Infarction Using Pre-clinical Magnetic Resonance Imaging[J]. Nihon Hoshasen Gijutsu Gakkai Zasshi, 2018, 74(7): 722-725
- [14] Zhu H, Zhao T, Liu J. Role of Paraoxonase 1 Activity and Oxidative/Antioxidative Stress Markers in Patients with Acute Cerebral Infarction[J]. Clin Lab, 2018, 64(6): 1049-1053
- [15] Iso T, Yanagawa Y, Takeuchi I, et al. Concomitance Acute Cerebral Infarction and Remote Intra-Cerebral Hemorrhaging on Arrival [J]. J Emerg Trauma Shock, 2018, 11(2): 149-150
- [16] Zhu H, Li Z, Lv J, et al. Effects of cerebral small vessel disease on the outcome of patients with ischemic stroke caused by large artery atherosclerosis[J]. Neurol Res, 2018, 40(5): 381-390
- [17] Anufriev PL, Evdokimenko AN, Gulevskaya TS. Cerebral infarctions in vertebrobasilar artery atherosclerosis [J]. Arkh Patol, 2018, 80(1): 3-10
- [18] Hirpara MR, Manikkath J, Sivakumar K, et al. Long circulating PE-Gylated-chitosan nanoparticles of rosuvastatin calcium: Development and in vitro and in vivo evaluations [J]. Int J Biol Macromol, 2018, 107(Pt B): 2190-2200
- [19] Ahsan MN, Prasad Verma PR. Solidified self nano-emulsifying drug delivery system of rosuvastatin calcium to treat diet-induced hyperlipidemia in rat: in vitro and in vivo evaluations[J]. Ther Deliv, 2017, 8(3): 125-136
- [20] Chung JW, Hwang J, Lee MJ, et al. Previous Statin Use and High-Resolution Magnetic Resonance Imaging Characteristics of Intracranial Atherosclerotic Plaque: The Intensive Statin Treatment in Acute Ischemic Stroke Patients with Intracranial Atherosclerosis Study[J]. Stroke, 2016, 47(7): 1789-1796
- [21] 贺曦,张敏,杨柳,等.瑞舒伐他汀钙对脑梗死患者动脉粥样硬化及脑血流动力学的改善作用研究[J].检验医学与临床, 2016, 13(16): 2276-2277
- [22] 冯志霞,许哲通,吕志坤,等.不同剂量瑞舒伐他汀钙联合丁苯肽氯化钠治疗青年脑梗死的疗效 [J]. 热带医学杂志, 2016, 16(9): 1156-1158
- [23] Ye Y, Nylander S, Birnbaum Y. Unraveling the Interaction of Aspirin, Ticagrelor, and Rosuvastatin on the Progression of Atherosclerosis and Inflammation in Diabetic Mice [J]. Cardiovasc Drugs Ther, 2017, 31(5-6): 489-500
- [24] You T, Liu XG, Hou XD, et al. Effect of statins on blood pressure: Analysis on adverse events released by FDA [J]. Clin Exp Hypertens, 2017, 39(4): 325-329
- [25] Jiao Y, Hu F, Zhang Z, et al. Efficacy and Safety of Loading-Dose Rosuvastatin Therapy in Elderly Patients with Acute Coronary Syndromes Undergoing Elective Percutaneous Coronary Intervention[J]. Clin Drug Investig, 2015, 35(12): 777-784

- Doppler ultrasonography in the diagnosis of cesarean scar pregnancy [J]. Chinese Practical Medicine, 2016, 11(21): 56-57
- [8] Kimberly Bannon, Carlos Fernandez, David Rojas, et al. Diagnosis and Management of Intramural Ectopic Pregnancy [J]. The Journal of Minimally Invasive Gynecology, 2013, 20(5): 697-700
- [9] 麦尔哈巴·麦麦提,艾斯凯尔·阿卜拉.腹部B超与阴道B超在异位妊娠诊断中的比较研究 [J]. 临床医药文献电子杂志, 2017, 4(41): 8036+8038
- [10] 李玲.经腹超声与阴道超声对异位妊娠诊断符合率的分析[J].医疗装备, 2016, 29(12): 36-37
- [11] R. A. Guzmán Rojas, K. L. Shek, S. M. Langer, et al. Prevalence of anal sphincter injury in primiparous women[J]. Ultrasound in Obstetrics & Gynecology, 2013, 42(4): 461-466
- [12] 李蒙森,石有振,郑瑜,等.经阴道三维超声联合断层超声显像技术在早期异位妊娠诊断中的应用 [J]. 中华医学超声杂志 (电子版), 2015, 12(02): 128-135
- [13] 臧煜,李冬.经腹部与经阴道彩色多普勒超声诊断早期异位妊娠的临床比较[J].影像研究与医学应用, 2018, 2(03): 97-98
- [14] W. Henrich, J. Stupin. 3D Volume Contrast Imaging (VCI) for the Visualization of Placenta Previa Increta and Uterine Wall Thickness in a Dichorionic Twin Pregnancy [J]. Ultraschall in Med, 2011, 32(04): 406-411
- [15] 范智媛,梁宏伟,张淋淋.经腹与经阴道超声在异位妊娠早期诊断中的效果比较[J].西部医学, 2015, 27(07): 1069-1070+1074
- [16] 樊莹,张春玲.经阴道彩色多普勒超声检测妊娠黄体在早期不明位置妊娠中的诊断价值 [J]. 临床医学研究与实践, 2019, 4(01): 136-137+147
- [17] B.J. Snell. Assessment and Management of Bleeding in the First Trimester of Pregnancy [J]. Journal of Midwifery and Women's Health, 2009, 54(6): 483-491
- [18] 王洪瑞.阴道彩色多普勒超声在早期异位妊娠中的应用[J].深圳中西医结合杂志, 2018, 28(16): 69-70
- [19] 庞慧贤,卫红艳,张海燕,等.经阴道彩色多普勒超声对异位妊娠及宫内早孕妊娠黄体的鉴别诊断 [J]. 临床医学工程, 2018, 25(12): 1585-1586
- [20] Grigoris F, Grimbizis, Dimitrios Tsolakidis, et al. A prospective comparison of transvaginal ultrasound, saline infusion sonohysterography, and diagnostic hysteroscopy in the evaluation of endometrial pathology [J]. Fertility and Sterility, 2010, 94(7): 2720-2725
- [21] 孙晓丹,吴壮雄,卢来顺.阴道彩色多普勒超声在早期异位妊娠诊断中的临床价值[J].中国当代医药, 2018, 25(21): 92-94
- [22] 李燕霞,陈燕娜.经阴道彩色多普勒超声对异位妊娠及早孕妊娠黄体的鉴别诊断价值[J].中国现代药物应用, 2018, 12(15): 60-61
- [23] E. Pilloni, M. G. Alemanno, P. Gaglioti, et al. Accuracy of ultrasound in antenatal diagnosis of placental attachment disorders[J]. Ultrasound in Obstetrics & Gynecology, 2016, 47(3): 302-307
- [24] 方燕璇,林小琼.探讨经腹部和经阴道彩色多普勒超声诊断早期异位妊娠的应用价值[J].广州医科大学学报, 2016, 44(1): 61-63
- [25] 辛燕,王婷婷.早期异位妊娠诊断中经阴道与经腹部彩色多普勒超声的对比研究[J].实用妇科内分泌电子杂志, 2018, 5(1): 63-64
- [26] R. Dankovcik, V. Vargova, K. Balasovicova, et al. Dudas. Visualization of sigmoidal diverticulosis during gynecological three-dimensional ultrasound examination [J]. Ultrasound in Obstetrics & Gynecology, 2013, 41(2): 231-232
- [27] 朱迅桦. 经腹部超声与经阴道彩色多普勒超声早期诊断宫外孕的对比[J].影像技术, 2018, 30(03): 20-22
- [28] 明婧,罗锦麟,明颖.经阴道三维超声联合断层超声显像技术在早期异位妊娠诊断中的价值分析[J].影像研究与医学应用, 2018, 2(08): 146-147
- [29] 奚嘉婧,梁政巧,柳玲.经腹彩色多普勒超声与经阴道超声在异位妊娠诊断中的对比分析[J].首都食品与医药, 2018, 25(14): 85-86
- [30] 吴艳春,李岚,张卫东,等.经阴道超声诊断陈旧性异位妊娠48例分析[J].现代医药卫生, 2011, 27(01): 107-108

(上接第 2750 页)

- [26] Chen H, Ding S, Liu X, et al. Association of Interleukin-6 Genetic Polymorphisms and Environment Factors Interactions with Coronary Artery Disease in a Chinese Han Population [J]. ClinExp Hypertens, 2018, 40(6): 272-276
- [27] Chang H, Lu Z. Analysis of Serum TNF- α , IL-6 and IL-8 Levels in Patients with Cerebral Infarction [J]. Medical Information, 2016, 28(3): 60-61
- [28] Wang J, Han D, Sun M, et al. A Combination of Remote Ischemic Preconditioning and Cerebral Ischemic Postconditioning Inhibits Autophagy to Attenuate Plasma HMGB1 and Induce Neuroprotection Against Stroke in Rat[J]. J Mol Neurosci, 2016, 58(4): 424-431
- [29] Umahara T, Uchihara T, Koyama S, et al. Local extension of HMGB1 in atherosclerotic lesions of human main cerebral and carotid arteries [J]. Histol Histopathol, 2014, 29(2): 235-242
- [30] Zhao L, Zhai Z, Hou W. Analysis of Carotid color ultrasonography and high sensitive C-reactive protein in patients with atherosclerotic cerebral infarction[J]. Pak J Med Sci, 2016, 32(4): 931-934