

doi: 10.13241/j.cnki.pmb.2019.09.036

异甘草酸镁对急性重症胰腺炎患者血清 CAM-1、SIL-2R、IL-2 水平及肝肾功能的影响 *

魏 鹏¹ 罗传铃¹ 宋 堃² 王 月¹ 陈方周³

(1 枣庄矿业集团中心医院 重症医学科 山东 枣庄 277000; 2 北京中医药大学枣庄医院 重症医学科 山东 枣庄 277000;

3 泰山医学院附属医院 重症医学科 山东 泰安 271000)

摘要 目的:探讨异甘草酸镁对急性重症胰腺炎患者血清细胞间粘附分子-1(CAM-1)、可溶性白细胞介素-2受体(SIL-2R)、白细胞介素-2(IL-2)水平及肝肾功能的影响。**方法:**选择2014年3月~2016年9月于我院接受治疗的86例急性重症胰腺炎患者,按随机数字表法分为对照组与实验组,每组43例。对照组选用常规治疗,实验组在常规治疗基础上加以异甘草酸镁治疗,两组均持续治疗14天。比较两组的临床疗效,治疗前后血清CAM-1、SIL-2R、IL-2、谷草转氨酶、谷丙转氨酶、尿素氮、血肌酐水平的变化及不良反应的发生情况。**结果:**治疗后,实验组总有效率为90.69%,显著高于对照组($P<0.05$);两组血清CAM-1、SIL-2R、IL-2、谷草转氨酶、谷丙转氨酶、尿素氮、血肌酐水平均较治疗前显著降低,且实验组以上指标均明显低于对照组($P<0.05$)。两组不良反应发生情况比较差异无统计学意义($P>0.05$)。**结论:**与常规治疗相比,异甘草酸镁可显著提高急性重症胰腺炎的临床效果,降低血清CAM-1、SIL-2R、IL-2水平,保护肝肾功能。

关键词:急性重症胰腺炎;异甘草酸镁;细胞间粘附分子-1;可溶性白细胞介素-2受体;白细胞介素-2

中图分类号:R576 **文献标识码:**A **文章编号:**1673-6273(2019)09-1766-04

Effect of Magnesium Isoglycyrrhizinate on the Serum Levels of CAM-1, SIL-2 R and IL-2, Liver and Kidney Function of Patients with Severe Acute Pancreatitis*

WEI Peng¹, LUO Chuan-ling¹, SONG Kun², WANG Yue¹, CHEN Fang-zhou³

(1 Department of critical care medicine, Central Hospital of Zaozhuang Mining Group, Zaozhuang, Shandong, 277000, China;

2 Department of critical care medicine, Zaozhuang hospital, Beijing University of Chinese Medicine, Zaozhuang, Shandong, 277000, China;

3 Department of critical care medicine, Affiliated Hospital of Tai'an Medical College, Tai'an, Shandong, 271000, China)

ABSTRACT Objective: To investigate the effect of magnesium isoglycyrrhizinate on the serum levels of Cell adhesion molecule-1 (CAM-1), soluble interleukin-2 receptor (SIL-2 R), interleukin-2 (IL-2) levels, liver and kidney function of patients with severe acute pancreatitis. **Methods:** 86 cases of patients with acute severe pancreatitis from March 2014 to September 2016 in our hospital were divided into the control group and the experimental group according to random number table method, with 43 cases in each group. The control group was given conventional treatment, while the experimental group was given magnesium isoglycyrrhizinate based on the control group, both groups were treated for 14 days. The curative effect, changes of serum levels of CAM-1, SIL-2 R and IL-2, aspartate aminotransferase, cereal third transaminase, urea nitrogen, serum creatinine before and after the treatment and the incidence of adverse reactions were compared between two groups. **Results:** After treatment, the total effective rate of experimental group was 90.69%, which was higher than that of the control group ($P<0.05$); the serum levels of CAM-1, SIL-2 R and IL-2, aspartate aminotransferase, cereal third transaminase, urea nitrogen, serum creatinine of two group were significantly reduced than those before treatment, which were all significantly lower in the experimental group than those of the control group ($P<0.05$). there was no difference in the occurrence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Magnesium isoglycyrrhizinate was more effective for severe acute pancreatitis than conventional treatment alone, which could decrease the serum levels of CAM-1, SIL-2 R and IL-2 and protect the liver and kidney function.

Key words: Acute severe pancreatitis; Magnesium isoglycyrrhizinate; Cell adhesion molecule-1; Soluble interleukin-2 receptor; Interleukin-2

Chinese Library Classification(CLC): R576 **Document code:** A

Article ID: 1673-6273(2019)09-1766-04

* 基金项目:山东省医药卫生科技发展计划项目(2015WS0502)

作者简介:魏鹏(1984-),男,本科,主治医师,研究方向:急危重症患者的救治,电话 13793702882, E-mail: liuwenshuai269@163.com

(收稿日期:2018-08-23 接受日期:2018-09-18)

前言

重症急性胰腺炎病情较为险恶,且有较高的病死率,主要是因暴饮暴食、酗酒等所致,能够诱导腹痛、高热、休克、呼吸异常等改变,同时可使肾脏、肝脏、呼吸及神经系统等功能受累,以肝肾功能障碍表现最为明显,未经及时治疗者甚至可危及患者的生命^[1,2]。尽早诊断重症胰腺炎并选用合理的治疗法是并发症减少及死亡率降低的关键,多项研究证实^[3,4]急性重症胰腺炎经常规治疗虽可一定程度的缓解临床症状,但难以得到良好的效果。

异甘草酸镁既往临床多应用于病毒性肝炎,不仅能够对肝细胞膜发挥保护作用,同时能够起到抗过敏、抗炎等作用,但其对急性重症胰腺炎的作用并不完全明确^[5,6]。国外研究显示^[7,8]炎症及细胞因子可于急性胰腺炎发病中起到关键作用,以细胞粘着因子-1(CAM-1)、白细胞介素-2(IL-2)及可溶性白细胞介素-2受体(SIL-2R)表现最为明显。本研究旨在探讨异甘草酸镁对急性重症胰腺炎患者血清 CAM-1、SIL-2R、IL-2 水平及肝肾功能的影响,以期异甘草酸镁用于临床治疗急性胰腺炎提供更多的参考依据。

1 资料与方法

1.1 一般资料

选择 2014 年 3 月~2016 年 9 月于我院接受治疗的 86 例急性重症胰腺炎患者。纳入标准:符合急性重症胰腺炎诊断标准^[9];伴急性胰腺炎改变,伴器官衰竭或者并发症;入院时间在发病 24 h 以内;意识清晰;无本研究药物禁忌症。排除标准:既往长时间接受糖皮质激素治疗;脏器功能明显病变;恶性肿瘤;手术指征者。按随机数字表法将所有患者分为对照组与实验组,每组 43 例。对照组年龄 23~67 岁,平均(47.08±6.23)岁;女

20 例,男 23 例。实验组年龄 22~65 岁,平均(46.21±6.75)岁;女 21 例,男 22 例。两组基础资料比较差异无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

对照组均予以常规基础治疗。实验组在其基础上联合异甘草酸镁治疗,将 100 mg 异甘草酸镁和 250 mL 10%葡萄糖注射液稀释予以患者静脉滴注,qd。两组均持续用药 14 天,期间评估疗效,并统计临床表现缓解时间和安全性。

1.3 观察指标

1.3.1 疗效观察 用药 5 天内临床体征及症状完全恢复,血常规及血淀粉酶未见异常即痊愈;用药 7 天内临床体征及症状完全恢复,血常规及血淀粉酶未见异常即显效;用药 10 天内临床体征及症状完全恢复,血常规及血淀粉酶未见异常即好转;用药时间在 10 天以上但上述指标仍未见改善者即无效。痊愈、显效及好转均为总有效^[10]。

1.3.2 血清指标测定 于用药前后收集患者外周静脉血 2 mL,常规分离血清,将上清液保留。CAM-1、SIL-2R、IL-2 予以放射免疫法进行。

1.4 统计学分析

数据处理选用 SPSS18.0 进行,计量资料以($\bar{x} \pm s$)表示,组间比较用 t 检验,计数资料以[(例)%]表示,组间比较用 χ^2 检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后,实验组总有效率为 90.69%,较对照组显著升高(74.42%, $P<0.05$),见表 1。

表 1 两组疗效比较[例(%)]

Table 1 Comparison the curative effect between two groups[n(%)]

Items	Control group(n=43)	Experimental group(n=43)
Cure	6(13.95)	12(27.91)
Effective	13(30.23)	17(39.53)
Improve	13(30.23)	10(23.26)
Invalid	11(25.57)	4(9.30)
Total effective rate	32(74.42)	39(90.69) ^a

Note: Compared with control group, ^a $P<0.05$.

2.2 两组临床表现缓解时间的比较

实验组临床表现如第一次排便时间、肠鸣音、腹痛、腹胀缓

解时间显著短于对照组($P<0.05$),见表 2。

表 2 两组临床表现缓解时间比较($\bar{x} \pm s$)

Table 2 Comparison of the relieve time of clinical symptoms between the two groups($\bar{x} \pm s$)

Items	Control group(n=43)	Experimental group(n=43)
Bowel sounds(h)	30.27±3.76	15.20±1.89 ^a
First defecation(h)	35.41±4.32	19.46±2.40 ^a
Stomach ache(d)	4.98±0.63	3.51±0.45 ^a
Bloating(d)	5.65±0.72	4.67±0.59 ^a

Note: Compared with control group, ^a $P<0.05$.

2.3 两组治疗前后血清 CAM-1、SIL-2R、IL-2 水平的比较

治疗前, 两组血清 CAM-1、SIL-2R、IL-2 水平比较差异无统计学意义($P>0.05$); 治疗后, 实验组血清 CAM-1、SIL-2R 水平

均较对照组显著降低($P<0.05$), 血清 IL-2 水平显著高于对照组 ($P<0.05$), 见表 3。

表 3 两组治疗前后血清 CAM-1、SIL-2R、IL-2 水平的变化($\bar{x} \pm s$)

Table 3 Comparison of the serum levels of CAM-1, SIL-2R and IL-2 between the two groups before and after treatment($\bar{x} \pm s$)

Items	Time	Control group(n=43)	Experimental group(n=43)
CAM-1($\mu\text{g/L}$)	Before treatment	456.23 $\pm$ 57.09	455.70 $\pm$ 56.21
	After treatment	311.58 $\pm$ 38.79 ^b	142.69 $\pm$ 17.35 ^{ab}
SIL-2R(ng/L)	Before treatment	126.30 $\pm$ 15.43	125.79 $\pm$ 16.72
	After treatment	73.29 $\pm$ 9.05 ^b	60.34 $\pm$ 7.90 ^{ab}
IL-2(ng/L)	Before treatment	76.45 $\pm$ 9.85	77.04 $\pm$ 8.73
	After treatment	120.98 $\pm$ 15.21 ^b	146.23 $\pm$ 18.27 ^{ab}

Note: Compared with the control group, ^a $P<0.05$; Compared with before treatment, ^b $P<0.05$.

2.4 两组治疗前后肝肾功能比较

两组治疗前肝肾功能比较差异无统计学意义($P>0.05$); 治疗

后, 实验组肝肾功能指标均显著低于对照组($P<0.05$), 见表 4。

表 4 两组治疗前后肝肾功能比较($\bar{x} \pm s$)

Table 4 Comparison of the liver and kidney function between the two groups before and after the treatment($\bar{x} \pm s$)

Items	Time	Control group(n=43)	Experimental group(n=43)
Aspartate aminotransferase(U/L)	Before treatment	201.66 $\pm$ 25.87	202.43 $\pm$ 24.31
	After treatment	45.21 $\pm$ 5.62 ^b	30.77 $\pm$ 3.53 ^{ab}
Cerebral third transaminase(U/L)	Before treatment	188.90 $\pm$ 23.60	187.65 $\pm$ 24.76
	After treatment	47.45 $\pm$ 5.86 ^b	32.11 $\pm$ 4.20 ^{ab}
Urea nitrogen(mmol/L)	Before treatment	13.25 $\pm$ 1.62	13.78 $\pm$ 1.37
	After treatment	8.90 $\pm$ 1.10 ^b	7.65 $\pm$ 0.97 ^{ab}
Serum creatinine($\mu\text{mol/L}$)	Before treatment	195.46 $\pm$ 24.33	193.70 $\pm$ 25.81
	After treatment	96.71 $\pm$ 12.11 ^b	83.22 $\pm$ 10.23 ^{ab}

Note: Compared with control group, ^a $P<0.05$; Compared with before treatment, ^b $P<0.05$.

2.5 两组不良反应发生情况的比较

治疗期间, 两组均未见严重不良反应。

3 讨论

急性重症胰腺炎病情危急, 目前缺乏明确特效疗法, 药物为其重要治疗手段^[11,12]。异甘草酸镁能够促进氧自由基的清除, 缓解炎症反应, 且可利于毛细血管的疏通^[13]。国外研究显示^[14,15]予异甘草酸镁治疗急性重症胰腺炎患者的临床效果肯定。本研究结果也显示异甘草酸镁治疗后的总有效率较高, 且能够明显缩短患者临床症状的缓解时间, 但具体机制尚未明确^[16,17]。

多种细胞因子在急性重症胰腺炎发病过程中发挥了关键作用, 可诱导血管发生渗漏, 血容量降低^[18,19]。同时, 多项临床研究证实受损的胰腺组织可作为一种炎症或者抗原刺激物导致机体免疫功能及细胞网络出现紊乱, 造成瀑布级别的炎症反应^[20,21]。CAM-1 主要于血管内皮细胞中表达, 能够调控血管内皮与白细胞之间的黏附, 诱导白细胞发生趋化, 刺激其释放大量的自由基及酶, 导致组织出现受损^[22,23]。SIL-2R 可影响活化淋巴细胞的活性, 导致免疫反应过度, 且可竞争性结合 IL-2, 抑制免疫功能^[24]。且 SIL-2R 可使 IgE 浓度及 B 淋巴功能受到影响, 降低机体免疫功能, 引起免疫逃逸。Th1 细胞受到多种因素因素刺激后能够分泌 IL-2, 提高细胞毒性, 调控免疫反应, 急性炎症

反应时其浓度明显降低^[25]。本研究显示治疗后两组血清 CAM-1、SIL-2R 均有显著下降, 但异甘草酸镁组以上指标降低更明显, 且血清 IL-2 水平明显增加, 提示联合异甘草酸镁治疗能够明显调节机体的炎症反应, 促进机体内环境的稳定, 从而有利于患者恢复。

急性重症胰腺炎发病期间由于氧自由基、炎性因子的大量聚集, 能够引起多个器官的功能发生衰竭, 其中对肝肾的影响较为明显。有关实验证实最早发生损伤的脏器即肝脏, 能够导致病情加重, 并对预后形成直接影响, 严重者能够进展为肝脏衰竭, 增加患者病死率^[26,27]。肝细胞受损时能够增加细胞膜的通透性, 诱导多种因子细胞因子到达血液, 引起肝脏功能减弱, 并为其其他器官损伤提供基础^[28]。临床研究报道急性重症胰腺炎患者多种因子浓度均显著增加, 随着患者病情的显著缓解, 其浓度明显下降。有研究指出 CAM-1 能够诱导单核细胞及白细胞对肾脏上皮细胞发生粘附作用, 导致毒性产物的堆积, 引起肾小球发生损伤, 尿素氮水平升高可提示伴慢性肾炎的可能^[29]。血肌酐是机体的肌肉代谢产物, 其水平与肾小球率过滤呈反比。两组治疗后肝肾功能指标均有一定改善, 但异甘草酸镁的变化幅度更大, 说明其有利于对脏器功能的保护, 减轻其损伤, 从而有效调整机体状态, 更有利于机体的恢复, 可能与其能够使肝细胞膜保持稳定有关^[30,31]。同时, 研究显示急性重症胰腺炎

治疗期间均未见明显不良反应,说明其安全性高,未增加患者的负担。

综上所述,与常规治疗相比,异甘草酸镁可显著提高急性重症胰腺炎的临床效果,降低血清 CAM-1、SIL-2R、IL-2 水平,保护肝肾功能。

参考文献(References)

- [1] Thandassery RB, Choudhary N, Bahl A, et al. Characterization of Cardiac Dysfunction by Echocardiography in Early Severe Acute Pancreatitis[J]. *Pancreas*, 2017, 46(5): 626-630
- [2] Portelli M, Jones CD. Severe acute pancreatitis: pathogenesis, diagnosis and surgical management[J]. *Hepatobiliary Pancreat Dis Int*, 2017, 16(2): 155-159
- [3] Srinivasan G, Venkatakrishnan L, Sambandam S, et al. Current concepts in the management of acute pancreatitis [J]. *J Family Med Prim Care*, 2016, 5(4): 752-758
- [4] Koutroumpakis E, Slivka A, Furlan A, et al. Management and outcomes of acute pancreatitis patients over the last decade: A US tertiary-center experience[J]. *Pancreatol*, 2017, 17(1): 32-40
- [5] Xu Q, Wang J, Chen F, et al. Protective role of magnesium isoglycyrrhizinate in non-alcoholic fatty liver disease and the associated molecular mechanisms[J]. *Int J Mol Med*, 2016, 38(1): 275-282
- [6] Uc A, Andersen DK, Bellin MD, et al. Chronic Pancreatitis in the 21st Century - Research Challenges and Opportunities: Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop[J]. *Pancreas*, 2016, 45(10): 1365-1375
- [7] Liu X, Guo X, Li J, et al. Interferon- γ Aggravated L-Arginine-Induced Acute Pancreatitis in Sprague-Dawley Rats and Its Possible Mechanism: Trypsinogen Activation and Autophagy Up-regulation [J]. *Pancreas*, 2017, 46(5): 619-625
- [8] Soyalt M, Yalcin M, Oter V, et al. Investigation of procalcitonin, IL-6, oxidative stress index (OSI) plasma and tissue levels in experimental mild and severe pancreatitis in rats[J]. *Bratisl Lek Listy*, 2017, 118(3): 137-141
- [9] Portelli M, Jones CD. Severe acute pancreatitis: pathogenesis, diagnosis and surgical management[J]. *Hepatobiliary Pancreat Dis Int*, 2017, 16(2): 155-159
- [10] Koutroumpakis E, Dasyam AK, Furlan A, et al. Isolated Peripancreatic Necrosis in Acute Pancreatitis Is Infrequent and Leads to Severe Clinical Course Only When Extensive: A Prospective Study From a US Tertiary Center[J]. *J Clin Gastroenterol*, 2016, 50(7): 589-595
- [11] Rathnakar SK, Vishnu VH, Muniyappa S, et al. Accuracy and Predictability of PANC-3 Scoring System over APACHE II in Acute Pancreatitis: A Prospective Study [J]. *J Clin Diagn Res*, 2017, 11(2): PC10-PC13
- [12] Ma M, Zhai CX, Sun CX. Correlations Between LP-PLA2 Gene Polymorphisms and Susceptibility and Severity of Acute Pancreatitis in a Chinese Population[J]. *Genet Test Mol Biomarkers*, 2017, 21(4): 206-212
- [13] Tang GH, Yang HY, Zhang JC, et al. Magnesium isoglycyrrhizinate inhibits inflammatory response through STAT3 pathway to protect remnant liver function [J]. *World J Gastroenterol*, 2015, 21(43): 12370-12380
- [14] Zheng J, Wu G, Hu GX, et al. Protective effects against and potential mechanisms underlying the effect of magnesium isoglycyrrhizinate in hypoxia-reoxygenation injury in rat liver cells [J]. *Genet Mol Res*, 2015, 14(4): 15453-15461
- [15] Watanabe K, Yoshifuji K, Ohkawa R, et al. Successful readministration of L-asparaginase after development of severe hypertriglyceridemia in a young adult with T-cell acute lymphoblastic leukemia [J]. *Rinsho Ketsueki*, 2018, 59(12): 2555-2560
- [16] Xie C, Li X, Wu J, et al. Anti-inflammatory Activity of Magnesium Isoglycyrrhizinate Through Inhibition of Phospholipase A2/Arachidonic Acid Pathway[J]. *Inflammation*, 2015, 38(4): 1639-1648
- [17] Huang X, Qin J, Lu S. Magnesium isoglycyrrhizinate protects hepatic L02 cells from ischemia/reperfusion induced injury[J]. *Int J Clin Exp Pathol*, 2014, 7(8): 4755-64
- [18] Xiong J, Wang K, Yuan C, et al. Luteolin protects mice from severe acute pancreatitis by exerting HO-1-mediated anti-inflammatory and antioxidant effects[J]. *Int J Mol Med*, 2017, 39(1): 113-125
- [19] Kaplan M, Ates I, Oztas E, et al. A New Marker to Determine Prognosis of Acute Pancreatitis: PLR and NLR Combination [J]. *J Med Biochem*, 2018, 37(1): 21-30
- [20] Grover AS, Kadiyala V, Banks PA, et al. The Utility of the Systemic Inflammatory Response Syndrome Score on Admission in Children With Acute Pancreatitis[J]. *Pancreas*, 2017, 46(1): 106-109
- [21] Wang WY, Chen Y, Su X, et al. Resistin-Like Molecule- α Causes Lung Injury in Rats with Acute Pancreatitis by Activating the PI-3K/Akt-NF- κ B Pathway and Promoting Inflammatory Cytokine Release[J]. *Curr Mol Med*, 2016, 16(7): 677-687
- [22] Wang P, Wang W, Shi Q, et al. Paeoniflorin ameliorates acute necrotizing pancreatitis and pancreatitis induced acute renal injury[J]. *Mol Med Rep*, 2016, 14(2): 1123-1131
- [23] Küçükçerem K, Ergin M, Kılınc İ, et al. The role of soluble urokinase plasminogen activator receptor (SuPAR) as an indicator of the severity of acute pancreatitis[J]. *Turk J Med Sci*, 2018, 48(6): 1175-1181
- [24] Signore A, Capriotti G, Chianelli M, et al. Detection of insulinitis by pancreatic scintigraphy with 99mTc-labeled IL-2 and MRI in patients with LADA (Action LADA 10) [J]. *Diabetes Care*, 2015, 38(4): 652-658
- [25] He F, Yao H, Xiao Z, et al. Inhibition of IL-2 inducible T-cell kinase alleviates T-cell activation and murine myocardial inflammation associated with CVB3 infection[J]. *Mol Immunol*, 2014, 59(1): 30-38
- [26] Zhang YM, Ren HY, Zhao XL, et al. Pharmacokinetics and pharmacodynamics of Da-Cheng-Qi decoction in the liver of rats with severe acute pancreatitis[J]. *World J Gastroenterol*, 2017, 23(8): 1367-1374
- [27] Elkhouly MA, Salazar MJ, Simons-Linares CR. Hypertriglyceridemia-Associated Drug-Induced Acute Pancreatitis [J]. *Pancreas*, 2019, 48(1): 22-35
- [28] Hu N, Shen Y, Liu F, et al. Morphological and immunobiochemical analysis of the liver in L-arginine induced experimental chronic pancreatitis[J]. *Pancreatol*, 2017, 17(2): 247-254
- [29] Tseng CW, Chen YT, Lin CL, et al. Association between chronic pancreatitis and pyogenic liver abscess: a nationwide population study [J]. *Curr Med Res Opin*, 2017, 33(3): 505-510
- [30] Yılmaz EM, Kandemir A. Significance of red blood cell distribution width and C-reactive protein/albumin levels in predicting prognosis of acute pancreatitis [J]. *Ulus Travma Acil Cerrahi Derg*, 2018, 24(6): 528-531
- [31] Mallick B, Shrama DJ, Siddappa P, et al. Differences between the outcome of recurrent acute pancreatitis and acute pancreatitis[J]. *JGH Open*, 2018, 2(4): 134-138