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## 免疫球蛋白联合磷酸肌酸钠对病毒性心肌炎患儿心肌重塑和心肌损伤的影响\*

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**摘要 目的:**研究免疫球蛋白联合磷酸肌酸钠对病毒性心肌炎患儿心肌重塑和心肌损伤的影响。**方法:**选择2017年1月~2019年12月我院收治的143例病毒性心肌炎患儿,随机分为两组。对照组静脉输注磷酸肌酸钠治疗,每次0.5~1.0 g,每天1次,连用14 d。观察组联合静脉注射人免疫球蛋白,剂量1 g/(kg·d),每天1次,连用2 d。检测两组治疗前后的心肌重塑指标和心肌损伤指标变化情况。**结果:**观察组的有效率明显高于对照组( $P<0.05$ );治疗前,两组的血清血清转化生长因子 $\beta 1$ (transforming growth factor- $\beta 1$ , TGF $\beta 1$ )、I型前胶原氨基端肽(nitrogen terminal propeptide of type I procollagen, PINP)、基质金属蛋白酶(matrix metalloproteinase-2, MMP2)、I型胶原吡啶交联终肽(type I collagen carboxy terminal telopeptide, ICTP)、MMP9水平无明显差异( $P>0.05$ ),治疗后,两组的血清TGF $\beta 1$ 、PINP、MMP2、ICTP、MMP9水平均明显降低( $P<0.05$ ),且观察组的血清TGF $\beta 1$ 、PINP、MMP2、ICTP、MMP9水平明显低于对照组( $P<0.05$ );治疗前,两组的血清血清丙二醛(malondialdehyde, MDA)、心肌肌钙蛋白I(Cardiac troponin, cTnI)、脑利钠肽(B-type natriuretic peptide, BNP)、肌酸激酶同工酶(Creatine kinase isoenzyme, CK-MB)水平无明显差异( $P>0.05$ ),治疗后,两组的血清MDA、CK-MB、BNP和cTnI水平均明显降低( $P<0.05$ ),且观察组的血清MDA、CK-MB、BNP和cTnI水平明显低于对照组( $P<0.05$ )。**结论:**免疫球蛋白联合磷酸肌酸钠对病毒性心肌炎患儿有显著的疗效,能有效抑制心肌重塑、减轻心肌损伤,值得进行推广。

**关键词:**免疫球蛋白;磷酸肌酸钠;病毒性心肌炎;心肌重塑;心肌损伤

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## Effect of Immunoglobulin Combined with Sodium Creatine Phosphate on Myocardial Remodeling and Myocardial Injury in Children with Viral Myocarditis\*

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**ABSTRACT Objective:** To investigate the effect of immunoglobulin combined with sodium creatine phosphate on myocardial remodeling and myocardial injury in children with viral myocarditis. **Methods:** Selected 143 cases of children with viral myocarditis who were treated in our hospital from January 2017 to December 2019, divided into two groups randomly. In the control group, sodium creatine phosphate was infused intravenously, 0.5~1.0 g each time, once a day for 14 days. The observation group combined with intravenous injection of human immunoglobulin at a dose of 1 g/(kg·d), once a day for 2 days. The changes of myocardial remodeling index and myocardial injury index were detected before and after treatment. **Results:** The effective rate of the observation group was significantly higher than control group ( $P<0.05$ ). Before treatment, there was no significant difference in the levels of TGF  $\beta 1$ , PINP, MMP2, ICTP and MMP9 between the two groups ( $P>0.05$ ), after treatment, the levels of TGF  $\beta 1$ , PINP, MMP2, ICTP and MMP9 in the two groups were significantly reduced ( $P<0.05$ ), the levels of TGF  $\beta 1$ , PINP, MMP2, ICTP and MMP9 in the observation group were significantly lower than those in the control group ( $P<0.05$ ). Before treatment, there was no significant difference in the levels of MDA, CK-MB, BNP and cTnI between the two groups ( $P>0.05$ ), after treatment, the levels of MDA, CK-MB, BNP and cTnI in the two groups were significantly reduced ( $P<0.05$ ), the levels of MDA, CK-MB, BNP and cTnI in the observation group were significantly lower than those in the control group ( $P<0.05$ ). **Conclusion:** Immunoglobulin combined with sodium creatine phosphate has a significant effect on children with viral myocarditis. It can effectively inhibit myocardial remodeling and reduce myocardial damage, which is worthy of promotion.

**Key words:** Immunoglobulin; Sodium Creatine Phosphate; Viral Myocarditis; Myocardial Remodeling; Myocardial Injury

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## 前言

病毒性心肌炎是由病毒感染(主要是柯萨奇病毒、流感病毒和脊髓灰质炎)所引起的以弥漫性或局限性的心肌非特异性间质性炎症病变为主的一种心肌炎性疾病<sup>[1]</sup>。部分患儿的起病较为隐匿,轻者无显著症状,急性重症患儿会发生心律失常、形成扩张型心肌病、心脏扩大,预后较差,威胁患儿的生命<sup>[2-4]</sup>。由于病毒性心肌炎的发病机制极为复杂,而且缺乏特效的抗病毒药物,该病尚无较好的治疗方法,目前主要采取抗病毒、抑制免疫反应以及营养心肌等疗法<sup>[5]</sup>。磷酸肌酸钠能有效缓冲肌肉中的酸性物质,缺氧时,能消耗葡萄糖无氧发酵过程中释放的氢离子,有效减轻酸中毒,抑制氧自由基的生成,改善心肌功能。磷酸肌酸钠虽能缓解病毒性心肌炎患儿的临床病症,但对心肌重塑的抑制效果并不显著。免疫球蛋白主要提取于大量混合的健康人血浆经不同方法提取的含多种抗细菌、病毒、寄生虫和支原体抗体的可供静脉注射的一种免疫球蛋白制品,能直接与患儿机体内的病毒相结合,有效清除机体内的病毒,对心肌细胞产生保护效果<sup>[6-9]</sup>。临床上关于免疫球蛋白与磷酸肌酸钠联合治疗病毒性心肌炎的报道比较少见。因此,本研究对其疗效进行了探讨,分析二者联用对病毒性心肌炎患儿血清心肌重塑指标和心肌损伤指标的影响,现报道如下。

## 1 资料与方法

### 1.1 一般资料

选择2017年1月~2019年12月我院收治的143例病毒性心肌炎患儿,纳入标准:(1)均经血液病毒特异性抗体,且结合患儿的症状确诊为病毒性心肌炎,(2)心功能Ⅱ~Ⅲ级,(3)均为首次接受治疗,(4)患儿的父母均知情同意。排除标准:(1)伴心功能衰竭的患儿;(2)合并先天性心脏病或心包积液的患儿;(3)伴精神疾患不能配合治疗的患儿;(4)对免疫球蛋白和磷酸肌酸钠过敏的患儿。用抽签法随机分为两组。观察组71例,男39例,女32例;年龄7个月~11岁,平均 $(6.14 \pm 1.29)$

岁;病程2~10 d,平均 $(4.27 \pm 1.36)$  d;心功能Ⅱ级患儿43例,心功能Ⅲ级患儿28例。对照组72例,男38例,女34例;年龄7个月~11岁,平均 $(6.07 \pm 1.36)$ 岁;病程2~10 d,平均 $(4.25 \pm 1.34)$  d;心功能Ⅱ级患儿43例,心功能Ⅲ级患儿29例。两组的基线资料具有可比性( $P>0.05$ )。

### 1.2 治疗方法

所有患儿均采取补充能量、抗病毒、维持酸碱电解质平衡、维生素C营养心肌等常规治疗,必要时采取强心、吸氧、利尿治疗。对照组:静脉输注磷酸肌酸钠(吉林英联生物制药,国药准字H20058621),每次0.5~1.0 g,每天1次,连用14 d。观察组联合静脉注射人免疫球蛋白(兰州生物制品研究所,国药准字S20023015),剂量1 g/(kg·d),每天1次,连用2 d。

### 1.3 观察指标

比较两组的治疗效果,评估标准<sup>[9]</sup>:①治愈:经过治疗后,患儿的心律基本正常,未见明显乏力、胸闷、水肿、心悸等表现,心功能、心肌酶和肌钙蛋白水平正常;②有效:经过治疗后,患儿偶见房室阻滞或者室速等异常心律,乏力、胸闷、水肿和心悸等症状与治疗前相比好转 $>50\%$ ,心功能、心肌酶和肌钙蛋白明显好转;③无效:经过治疗后,患儿出现反复、心律持续异常,或乏力、胸闷、水肿和心悸等症状未见好转,心功能没有改善,心肌酶维持高水平状态。

治疗前和治疗后14 d,采集患儿3 mL上肢静脉血,采用ELISA法检测血清TGFβ1、PINP、MMP2、ICTP、MMP9、MDA、cTnI、BNP、CK-MB水平,试剂盒均购自国药集团公司。

### 1.4 统计学分析

应用SPSS 21.0,两组间计量资料用 $(\bar{x} \pm s)$ 表示,对比用t检验,计数资料用%表示,对比用 $\chi^2$ 检验, $P<0.05$ 有统计学意义。

## 2 结果

### 2.1 疗效对比

观察组的有效率为94.37%,明显高于对照组72.22% ( $P<0.05$ ),见表1。

表1 疗效比较[例(%)]

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

| Groups            | n  | Cure      | Valid     | Invalid   | The total effect rate |
|-------------------|----|-----------|-----------|-----------|-----------------------|
| Control group     | 72 | 31(43.05) | 21(29.17) | 20(27.78) | 52(72.22)             |
| Observation group | 71 | 40(56.33) | 27(38.03) | 4(5.63)   | 67(94.37)*            |

Note: Compared with the control group, \* $P<0.05$ .

### 2.2 两组治疗前后的心肌重塑指标对比

治疗前,两组的血清TGFβ1、PINP、MMP2、ICTP、MMP9水平无明显差异( $P>0.05$ ),治疗后,两组的血清TGFβ1、PINP、

MMP2、ICTP、MMP9水平均明显降低( $P<0.05$ ),且观察组的血清TGFβ1、PINP、MMP2、ICTP、MMP9水平明显低于对照组( $P<0.05$ ),见表2。

表2 两组治疗前后的心肌重塑指标对比( $\bar{x} \pm s$ , ng/mL)

Table 2 Comparison of myocardial remodeling indexes between the two groups before and after treatment ( $\bar{x} \pm s$ , ng/mL)

| Groups            | n  |                  | TGFβ1                    | PINP                       | MMP2                       | ICTP                     | MMP9                      |
|-------------------|----|------------------|--------------------------|----------------------------|----------------------------|--------------------------|---------------------------|
| Control group     | 72 | Before treatment | 12.79± 2.34              | 75.31± 12.48               | 88.27± 13.48               | 11.73± 2.24              | 75.38± 11.34              |
|                   |    | After treatment  | 7.83± 1.56 <sup>#</sup>  | 45.29± 10.43 <sup>#</sup>  | 61.43± 11.37 <sup>#</sup>  | 7.44± 1.38 <sup>#</sup>  | 46.89± 10.34 <sup>#</sup> |
| Observation group | 71 | Before treatment | 12.83± 2.57              | 76.14± 13.59               | 89.16± 12.27               | 11.93± 2.49              | 76.19± 12.25              |
|                   |    | After treatment  | 5.29± 1.32 <sup>*#</sup> | 33.57± 10.14 <sup>**</sup> | 42.65± 10.48 <sup>**</sup> | 5.18± 1.24 <sup>*#</sup> | 37.28± 5.49 <sup>**</sup> |

Note: Compared with the control group, \* $P<0.05$ ; compared with before treatment, <sup>#</sup> $P<0.05$ .

### 2.3 两组治疗前后的心肌损伤指标对比

治疗前, 两组的血清血清 MDA、CK-MB、BNP 和 cTnI 水平无明显差异( $P>0.05$ ), 治疗后, 两组的血清 MDA、CK-MB、

BNP 和 cTnI 水平均明显降低 ( $P<0.05$ ), 且观察组的血清 MDA、CK-MB、BNP 和 cTnI 水平明显低于对照组( $P<0.05$ ), 见表 3。

表 3 两组治疗前后的心肌损伤指标对比( $\bar{x} \pm s$ )

Table 3 Comparison of myocardial injury indexes between the two groups before and after treatment ( $\bar{x} \pm s$ )

| Groups            | n  |                  | MDA(mmol/L)              | CK-MB(U/L)                | BNP(pg/mL)                  | cTnI(ng/mL)              |
|-------------------|----|------------------|--------------------------|---------------------------|-----------------------------|--------------------------|
| Control group     | 72 | Before treatment | 14.31± 2.78              | 36.25± 4.13               | 293.75± 24.38               | 0.61± 0.14               |
|                   |    | After treatment  | 8.34± 1.52 <sup>#</sup>  | 19.34± 2.21 <sup>#</sup>  | 164.57± 15.32 <sup>#</sup>  | 0.27± 0.05 <sup>#</sup>  |
| Observation group | 71 | Before treatment | 14.29± 3.17              | 37.28± 3.89               | 292.64± 25.63               | 0.62± 0.13               |
|                   |    | After treatment  | 5.67± 1.22 <sup>*#</sup> | 11.28± 1.36 <sup>*#</sup> | 105.82± 11.34 <sup>*#</sup> | 0.14± 0.02 <sup>*#</sup> |

Note: Compared with the control group, <sup>\*</sup> $P<0.05$ ; compared with before treatment, <sup>#</sup> $P<0.05$ .

### 3 讨论

病毒性心肌炎若未及时治疗会引起心力衰竭、心源性休克和心律失常等并发症, 损坏患儿的免疫系统功能, 甚至威胁生命安全<sup>[10-12]</sup>。病毒性心肌炎的病理过程比较复杂, 病毒能直接侵入患儿心肌, 导致心肌细胞坏死, 而且大量复制的病毒会对患儿的免疫系统造成损伤, 引起心肌功能减退和心肌细胞丢失<sup>[13]</sup>。心肌受到感染后会引发免疫反应所介导的氧自由基损害以及心肌细胞损害等, 最终造成患儿的心肌出现大面积坏死, 间质单核细胞大量浸润, 严重损害心功能<sup>[14,15]</sup>。因为小儿的免疫功能还未发育完善, 自身的抵抗能力较差, 因此, 与成人相比, 心肌炎的危害性更高, 不利于患儿的健康成长。

免疫球蛋白主要包含细菌的 IgG 抗体、大量广谱抗病毒等成份, 其具有识别抗原和清除抗原的生物学功能, 能对免疫反应进行有效的调节<sup>[16-20]</sup>。免疫球蛋白具有免疫抑制的双重调节性, 在机体的细胞免疫反应及体液免疫反应中具有重要的作用, 可以通过特异性地中和抗体, 有效抑制病毒的复制; 对机体内单核-巨噬细胞免疫廓清抗体的生成进行明显的抑制, 从而减轻心肌的炎性反应, 保护心肌细胞<sup>[21-24]</sup>。人免疫球蛋白的作用机制主要有 6 个方面: ① 中和自身抗体; ② 调节细胞的增殖以及凋亡; ③ 中和细胞因子; ④ 抑制 T 淋巴细胞的活化; ⑤ 抑制细胞的黏附作用; ⑥ 抑制抗体依赖细胞所介导的细胞毒性作用。磷酸肌酸钠作为一种高供能的物质, 能快速地改善机体心肌细胞的能量代谢<sup>[25]</sup>。本研究表明, 将免疫球蛋白与磷酸肌酸钠联用能抑制病毒和感染性细菌, 增强机体的调理功能和抗感染能力, 从而能减轻患儿的症状。

免疫球蛋白能够显著的提高病毒性心肌炎患儿的疗效。姜雪等<sup>[26]</sup>在常规治疗的基础上联用免疫球蛋白, 有效率明显升高。与本研究结果一致。其原因为, 免疫球蛋白富含多种抗细菌以及病毒的特异性抗体, 可有效的抑制感染机体心肌重塑过程。ICTP 及 PINP 分别是 I 型胶原分解代谢以及合成代谢的产物<sup>[27]</sup>。MMP2 及 MMP9 可以有效调控心肌间质内 I 型胶原的代谢过程。TGFβ1 可以通过下游的 Smad2/3 通路使胶原的分解代谢速度加快<sup>[28]</sup>。观察组的血清 TGFβ1、PINP、MMP2、ICTP、MMP9 水平明显低于对照组。表明在磷酸肌酸钠的基础上联用免疫球蛋白可以更加明显的抑制患儿病程中的心肌重塑。cTnI 在心肌细胞骨架结构的形成中有重要作用, CK-MB 能

调控心肌细胞内的能量代谢过程, 病毒性心肌炎的病程中由于心肌细胞受到破坏, 会导致 cTnI 及 CK-MB 的释放量明显增多。BNP 是机体内的心室肌细胞受牵拉后而分泌出的一种产物, 可以反映病毒性心肌炎发病过程中机体心功能的改变<sup>[29]</sup>。MDA 可以反映心肌受到氧化应激损伤的程度<sup>[30]</sup>。治疗后, 两组的血清 MDA、CK-MB、BNP 和 cTnI 水平均明显降低, 且观察组的血清 MDA、CK-MB、BNP 和 cTnI 水平明显低于对照组。表明在磷酸肌酸钠的基础上联用免疫球蛋白可以更加明显的减轻患儿病程中的心肌细胞损伤。

综上所述, 免疫球蛋白联合磷酸肌酸钠对病毒性心肌炎患儿有显著的疗效, 能有效抑制心肌重塑、减轻心肌损伤, 值得临床推广应用。

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