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心脉隆注射液联合重组人脑钠肽治疗慢性心衰患者的临床观察*

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摘要 目的: 探讨心脉隆注射液联合重组人脑钠肽治疗慢性心衰患者的临床效果及对患者心功能、血清 N 端脑钠肽前体 (N-terminal pro b-type natriuretic peptide, NT-proBNP)、胶原、一氧化氮(Nitric oxide, NO)、内皮素-1(endothelin-1, ET-1)水平的影响。**方法:** 选择 2015 年 1 月至 2017 年 5 月在我院治疗的慢性心衰患者 80 例, 根据随机数字法将其分为对照组和观察组。对照组采用重组人脑钠肽静脉治疗, 观察组在此基础上加用心脉隆注射液, 治疗 14 天。观察和比较两组患者治疗前后的心功能指标、血清 NT-proBNP、胶原、NO、ET-1 水平的变化、临床疗效及不良反应的发生情况。**结果:** 治疗后, 观察组总有效率为 97.5%, 显著高于对照组(82.5%, $P < 0.05$)。治疗前, 两组左心射血分数(left ventricular ejection fraction, LVEF)、每搏输出量(SV, Stroke volume)、心脏指数(CI, Cardiac index)、心率(HR, heart rate)、血清 NT-proBNP、NO、ET-1、胶原水平比较差异均无统计学意义($P > 0.05$); 治疗后, 两组 LVEF、SV、CI、NO 均较治疗前明显升高($P < 0.05$), 血清 NT-proBNP、ET-1、胶原水平均较治疗前明显下降($P < 0.05$), 且观察组治疗前后各指标的变化幅度均显著高于对照组($P < 0.05$)。在治疗过程中, 对照组出现 1 例低血压, 2 例头疼, 1 例恶心, 不良反应发生率为 10%; 观察组出现 1 例头痛, 不良反应发生率为 2.5%, 但两组不良反应发生率比较差异无统计学意义($P > 0.05$)。**结论:** 心脉隆注射液联合重组人脑钠肽治疗慢性心衰的临床疗效显著优于重组人脑钠肽静脉治疗, 其可有效降低患者血清 NT-proBNP、胶原、ET-1 的水平并升高血清 NO 的水平、改善患者心功能, 且安全性更高。

关键词: 慢性心衰; 心脉隆注射液; 重组人脑钠肽; 临床疗效

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Clinical Efficacy of Xinmailong Injection Combined with Recombinant Human Brain Natriuretic Peptide in the Treatment of Chronic Heart Failure*

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ABSTRACT Objective: To investigate the clinical efficacy of Xinmailong injection combined with recombinant human brain natriuretic peptide (rhBNP) in the treatment of patients with chronic heart failure and effect on the serum N-terminal pro-brain natriuretic peptide (NT-proBNP), type I procollagen carboxy terminal peptide (PICP), type III procollagen amino terminal peptide (PIIINP), nitric oxide (NO), endothelin-1 (ET-1) levels. **Methods:** Eighty patients with chronic heart failure were selected in our hospital from January 2015 to May 2017 and divided into the control group and the observation group according to the random number method. The control group was treated with rhBNP, while the observation group was treated with xinmailong injection combined with rhBNP. After two weeks of treatment, the clinical efficacy, incidence of adverse reactions and the changes of serum NT-proBNP, PICP, PIIINP, NO and ET-1 levels in the serum were compared before and after treatment between two groups. **Results:** After treatment, the total effective rate was 97.5% in the treatment group, which was significantly higher than 82.5% in the control group ($P < 0.05$). There was no significant difference in the LVEF, SV, CI, HR, serum NT-proBNP, NO, ET-1, PICP and PIIINP levels between the two groups before treatment ($P > 0.05$). After treatment, the levels of LVEF, SV, CI and NO were significantly increased ($P < 0.05$). And the levels of serum NT-proBNP, ET-1, PICP and PIIINP were significantly decreased ($P < 0.05$). The changes of indexes in the observation group were significantly higher than those in the control group after treatment ($P < 0.05$). During treatment, the control group showed 1 case of hypotension, 2 cases of headache, 1 case of nausea, and observation group only showed 1 case of headache. The incidence of adverse reactions in observation group was 2.5%, which was lower than 10% of control group with no significant difference ($P > 0.05$). **Conclusion:** Xinmailong injection combined with recombinant human brain natriuretic peptide was more effective in the treatment of heart failure than recombinant human brain natriuretic peptide alone, it could reduce the serum levels of NT-proBNP, collagen, ET-1 and increase the serum level of NO, improve the cardiac function without serious adverse reactions.

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慢性心力衰竭是各种因素诱发的心功能失代偿疾病,临床上也称为慢性充血性心力衰竭,具有病程长、治疗难、易反复且致死率高等特点^[1]。随着我国人口老龄化的加剧,该病的发病率与病死率逐年越高^[2]。有统计数据示^[3]2010年至2012年间,我国心衰患者的住院病死率高达5.3%。研究表明^[4]重组人脑钠肽治疗慢性心力衰竭的疗效确切。据报道^[5],心脉隆注射液也逐渐应用于慢性心力衰竭的治疗中。本研究采用心脉隆注射液联合重组人脑钠肽对慢性心力衰竭患者进行治疗,评估其对心功能的改善作用,以期慢性心力衰竭的治疗提供一定的临床依据。

1 资料与方法

1.1 一般资料

选择2015年11月至2017年5月无锡市第四人民医院收治的慢性心力衰竭患者80例,经过临床心内科医师诊断均符合慢性心力衰竭的诊断标准^[6]。所有患者不具有肝、肾、肺等其他器质性病变及恶性肿瘤等,无心源性休克及先天性心脏病等。所有纳入标准的患者均签订知情同意书。采用随机数字表法将纳入标准的80例患者分为对照组和观察组,各40例。对照组男性21例,女性19例,年龄45~78岁,平均年龄(64.75±5.25)岁,体重47~69 kg,平均体重(57.82±6.41) kg,病程2年~14年,平均病程(6.47±4.53)年。其中,心功能II级3例,心功能III级24例,心功能IV级13例。冠状动脉硬化性心脏病患者14例,风湿性心脏病患者1例,高血压性心脏病9例,扩张性心肌病6例,缺血性心肌病6例,慢性肺源性心脏病4例。观察组男性22例,女性18例,年龄44~79岁,平均年龄(65.35±6.15)岁,体重48~69 kg,平均体重(58.42±6.57) kg,病程2年~15年,平均病程(7.14±4.76)年。其中,心功能II级3例,心功能III级25例,心功能IV级12例。冠状动脉硬化性心脏病患者13例,风湿性心脏病患者2例,高血压性心脏病8例,扩张性心肌病7例,缺血性心肌病5例,慢性肺源性心脏病5例。两组患者一般资料比较差异均无统计学意义($P>0.05$),具有临床可比性。

1.2 治疗方法

所有患者在入院时均采用心衰常规治疗。对照组采用重组人脑钠肽负荷量1.5 μg/kg进行静脉滴注治疗^[7],随后保持0.01 μg/kg

连续输注7天。观察组在对照组基础上加用心脉隆注射液静脉滴注治疗^[7],剂量为5 mg/kg,加200 mL生理盐水,滴速20~40滴/分。上午8点和下午4点各静滴一次。两组治疗周期为14天。

1.3 观察指标

(1)心功能测定:治疗前和治疗2周后采用超声心动图测量两组患者的左心室射血分数(LVEF)、每搏量(SV)、心脏指数(CI)及心率(HR),评价心功能改善情况;(2)NT-proBNP、ET-1、NO、血清胶原水平测定:抽取静脉血5 mL于无抗凝剂的洁净试管中,静置2 h后,置于离心机中,4℃下3000 rpm离心10 min,取上层血清,采用酶联免疫吸附法测定血清中一氧化氮(NO)、内皮素-1(ET-1)、I型前胶原羧基端肽(PICP)、III型前胶原氨基端肽(PIIINP)的浓度,严格按照相关试剂盒(试剂盒由南京建成生物有限公司)说明书中的实验操作进行,并采用免疫定量分析仪(南京基蛋生物科技有限公司,南京)检测血清中NT-proBNP的水平;(3)不良反应监测:治疗期间观察并记录两组患者的不良反应发生情况。

1.4 疗效评定

疗效评定标准分为显效、有效及无效。心功能改善2级及以上,患者临床症状基本消失,生命体征基本恢复正常,心功能及心率基本恢复正常则判定为显效;心功能改善1级,患者临床症状及生命体征部分好转,心功能及心率有所改善则判定为有效;心功能改善不足1级,患者症状及体征无改善或加重则判定为无效。总有效率=(显效+有效)/总数*100。

1.5 统计学分析

计量资料数据采用SPSS19.0软件进行统计学分析,以平均值±标准差($\bar{x} \pm s$)表示,多组间比较采用t检验;计数资料采用百分比(%)表示,采用卡方 χ^2 检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 两组患者临床疗效的比较

如表1所示,对照组40例患者中,16例显效,占比40.0%,17例有效,占比42.5%,总有效率为82.5%;观察组40例患者,20例显效,占比50.0%,19例有效,占比47.5%,总有效率为97.5%。观察组总有效率显著高于对照组($P<0.05$)。

表1 两组患者临床疗效的比较[例(%)]

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

Groups	n	Excellent	Effective	Invalid	Total effective rate
Observation group	40	20(50.0)	19(47.5)	1(2.5)	39(97.5)
Control group	40	16(40.0)	17(42.5)	7(17.5)	33(82.5)
<i>P</i>		0.025	0.154	0.004	0.008

2.2 两组患者治疗前后心功能的比较

治疗前,两组患者LVEF、SV、CI、HR比较差异无统计学意

义($P>0.05$)。治疗后,对照组患者LVEF、SV、CI分别为(47.2±4.4)%、(45.1±4.3)mL、(3.4±0.5)L(min·m²)⁻¹,较治疗前明显升

高($P<0.05$),HR 为(79.8 ± 8.5)次/min,较治疗前明显下降($P<0.05$);观察组患者 LVEF、SV、CI 分别为(54.6 ± 4.6)%、(56.3 ± 5.0)mL、(4.5 ± 0.4)L(min $\cdot$ m 2) $^{-1}$,较治疗前明显升高($P<0.05$),HR 为 69.5 次/min,较治疗前明显下降($P<0.05$)。观察组治疗前后 LVEF、SV、CI、HR 的变化幅度高于对照组($P<0.05$),详见表 2。

表 2 两组患者治疗前后心功能指标的比较结果($\bar{x}\pm s$)Table 2 Comparison of heart function index between two groups before and after treatment($\bar{x}\pm s$)

Groups	Time	LVEF(%)	SV(mL)	CI[L(min $\cdot$ m 2) $^{-1}$]	HR(次/min)
Control group	Before treatment	34.3 $\pm$ 3.6	34.4 $\pm$ 3.3	2.3 $\pm$ 0.3	98.3 $\pm$ 10.1
	After treatment	47.2 $\pm$ 4.4 [#]	45.1 $\pm$ 4.3 [#]	3.4 $\pm$ 0.5 [#]	79.8 $\pm$ 8.5 [#]
Observation group	Before treatment	34.8 $\pm$ 3.5	34 $\pm$ 4.1	2.4 $\pm$ 0.2	98.6 $\pm$ 9.3
	After treatment	54.6 $\pm$ 4.6 ^{*,#}	56.3 $\pm$ 5.0 ^{*,#}	4.5 $\pm$ 0.4 ^{*,#}	69.4 $\pm$ 7.4 ^{*,#}

Note: compared with the control group, * $P<0.05$; compared with the same group before treatment, [#] $P<0.05$.

2.3 两组患者治疗前后血清 NT-proBNP、NO、ET-1 水平的比较

治疗前,两组患者血清 NT-proBNP、NO、ET-1 水平比较差异无统计学意义($P>0.05$)。治疗后,对照组患者血清 NT-proBNP、ET-1 的水平分别为 (1.68 ± 0.16)mg/L、(63.58 ± 6.14)ng/L,均显著低于治疗前($P<0.05$),血清 NO 的水平为(67.93 ± 6.25)

μ mol/L,显著高于治疗前($P<0.05$);观察组患者血清 NT-proBNP、ET-1 的水平分别为 (1.32 ± 0.15)mg/L、(75.46 ± 7.27)ng/L,均显著低于治疗前($P<0.05$),血清 NO 的水平为(49.81 ± 5.13) μ mol/L,显著高于治疗前($P<0.05$)。观察组治疗前后各指标的变化幅度显著高于对照组,差异有统计学意义($P<0.05$)。见表3。

表 3 两组患者血清 NT-proBNP、NO、ET-1 水平的比较结果($\bar{x}\pm s$)Table 3 Comparison of the serum NT-proBNP, NO and ET-1 levels between two groups before and after treatment($\bar{x}\pm s$)

Groups	n	Time	NT-proBNP(mg/L)	NO(μ mol/L)	ET-1(ng/L)
Control group	40	Before treatment	2.37 $\pm$ 0.19	55.85 $\pm$ 5.37	79.39 $\pm$ 6.72
		After treatment	1.68 $\pm$ 0.16	67.93 $\pm$ 6.25	63.58 $\pm$ 6.14
Observation group	40	Before treatment	2.38 $\pm$ 0.21	56.19 $\pm$ 5.38	80.14 $\pm$ 8.04
		After treatment	1.32 $\pm$ 0.15	75.46 $\pm$ 7.27	49.81 $\pm$ 5.13

Note: compared with the control group, * $P<0.05$; compared with the same group before treatment, [#] $P<0.05$.

2.4 两组患者治疗前后血清胶原水平的比较

治疗前,两组患者血清 PICP、PIIINP 水平比较差异无统计学意义($P>0.05$)。治疗后,对照组患者血清 PICP、PIIINP 水平分别为(81.48 ± 7.94) μ g/L、(4.06 ± 0.41) μ g/L,均显著低于治疗前

($P<0.05$); 观察组患者血清 PICP、PIIINP 的水平分别为 (66.43 ± 6.27) μ g/L、(3.21 ± 0.28) μ g/L,均显著低于治疗前 ($P<0.05$)。观察组患者治疗前后血清中该指标水平的变化幅度显著高于对照组($P<0.05$)。见表 4。

表 4 两组患者治疗前后血清胶原水平的比较结果($\bar{x}\pm s$)Table 4 Comparison of the serum PICP and PIIINP levels between two groups before and after treatment ($\bar{x}\pm s$)

Groups	n	Times	PICP	PIIINP
Control group	40	Before treatment	139.73 $\pm$ 12.41	6.73 $\pm$ 0.52
		After treatment	81.48 $\pm$ 7.94 [#]	4.06 $\pm$ 0.41 [#]
Observation group	40	Before treatment	140.05 $\pm$ 13.28	6.69 $\pm$ 0.63
		After treatment	66.43 $\pm$ 6.27 ^{*,#}	3.21 $\pm$ 0.28 ^{*,#}

Note: compared with the control group, * $P<0.05$; compared with the same group before treatment, [#] $P<0.05$.

2.5 两组患者不良反应发生情况的比较

在治疗过程中,对照组出现 1 例低血压,2 例头疼,1 例恶心,不良反应发生率为 10%;观察组出现 1 例头痛,不良反应发生率为 2.5%,两组不良反应发生率之间的差异无统计学意义($P>0.05$)。且经过相应处理后,各不良反应均消退。见表 5。

性临床慢性综合征,其临床症状主要表现为呼吸困难、体液滞留、身体乏力、咳嗽等^[8,9],治疗难、治疗效果差且病死率高,是心血管疾病引起死亡的重要原因之一。该病的发生发展机制包括细胞因子、氧化应激、心肌细胞凋亡、神经体液机制、血管内皮功能异常等^[10-13],各机制各具特点又相互联系,在慢性心力衰竭的发生和进程中均占重要地位,而从病因方面来控制疾病的进展是药物研究与开发的关键。慢性心力衰竭在临床上的治疗手段以药物治疗为主,包括醛固酮受体拮抗剂、利尿剂、A-

3 讨论

慢性心力衰竭是由各种因素引起的心脏功能减退的进行

表 5 两组患者不良反应发生情况的比较结果[例(%)]

Table 5 Comparison of incidence of adverse reactions between two groups[n (%)]

Groups	n	Low blood pressure	headache	nausea	Adverse reaction rate
Control group	40	1(2.5)	2(5)	1(2.5)	4(10)
Observation group	40	0(0)	1(2.5)	0(0)	1(2.5)*

Note: the treatment group compared with the control group, * $P>0.05$.

CEI/ARB、 β -受体阻滞剂、洋地黄等多种药物^[14,15]。rhBNP是由猪脑中分离的多肽类物质，可发挥醛固酮受体拮抗剂的活性，并具有排钠利尿、降低血管张力、阻滞神经内分泌等作用^[16,17]，可明显缓解慢性心力衰竭的临床症状。研究表明心力衰竭患者体内会出现内源性BNP代偿性增多，但是病理状态下BNP的分泌有限，不足以抑制交感神经系统的激活，因此补充外源性BNP可能对缓解心力衰竭的症状具有一定的作用。而近年来，多项研究证实^[4,18]rhBNP治疗慢性心力衰竭的疗效确切。

心脉隆注射液为国内新研发的慢性心力衰竭的辅助用药。近年来多项研究表明心脉隆注射液在心血管系统疾病的治疗方面具有种药理作用，如增加心肌收缩力、增加冠脉血流量、利尿作用、降低心脏前后负荷、抗心律失常等^[19]。因此，心脉隆注射液的作用与rhBNP可相互补充。本研究采用心脉隆注射液联合重组人脑钠肽对慢性心衰患者进行治疗，结果显示联合治疗的有效率可达97.5%，显著高于重组人脑钠肽单独治疗的82.5%，且患者经联合治疗后心功能的改善程度高于重组人脑钠肽单独治疗，说明心脉隆注射液联合重组人脑钠肽治疗慢性心力衰竭的疗效更佳。

NO为内皮衍生舒张因子，具有促进血管扩张、抑制血小板凝聚、改善血液微循环等作用，而ET-1可拮抗NO发挥作用。NO、ET-1均为血管内皮细胞功能的标志性细胞因子。有研究显示^[20]慢性心力衰竭患者体内血浆NO水平越低及ET-1水平越高，患者病情越严重。NT-proBNP为评价慢性心力衰竭患者治疗效果与预后的神经内分泌指标。有文献表明^[21]慢性心力衰竭患者血清中NT-proBNP浓度随着病情加重而升高。心脏胶原主要为I型胶原与III型胶原，对维持心脏结构和心功能中起着重要作用，其在体内过量蓄积可引起心肌间质纤维化，影响心肌的正常收缩与舒张功能，为导致慢性心衰的重要原因之一^[22]。本研究结果显示心脉隆注射液联合重组人脑钠肽能显著降低患者血清中NT-proBNP、血清胶原、ET-1的水平，升高NO的水平，且效果优于重组人脑钠肽单独治疗。

综上所述，心脉隆注射液联合重组人脑钠肽治疗慢性心衰的临床疗效显著优于重组人脑钠肽静脉治疗，其可有效降低患者血清NT-proBNP、胶原、ET-1的水平并升高血清NO的水平、改善患者心功能，且安全性更高。

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(上接第 4264 页)

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