·临床研究·

托伐普坦对老年心力衰竭患者心功能和神经内分泌因子的影响

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【摘 要】 目的 研究托伐普坦对心功能和神经内分泌因子的影响。**方法** 回顾性分析2017年1月至2019年1月陕西省人民医院心血管内科老年心力衰竭患者84例,根据利尿剂药物不同分为呋塞米组和托伐普坦组,每组42例,用药2周后比较2组患者心功能指标和脑钠肽(BNP)、内皮素(ET)及β-内啡肽水平。应用SPSS 18.0统计软件对数据进行分析。依据数据类型采用t检验或χ^2检验进行组间比较。**结果** 与治疗前相比,2组患者治疗后左心室射血分数(LVEF)和6 min步行距离水平升高,左心室收缩末期内径(LVESD)、左心室舒张末期内径(LVEDD)、心率、BNP、ET和β-内啡肽水平降低,且托伐普坦组治疗后较呋塞米组患者LVEF[(45.77±3.41)%和(40.82±4.09)%]、6 min步行距离[(474.51±8.45)和(395.90±6.48)m]、LVESD[(41.09±3.47)和(45.63±4.55)mm]、LVEDD[(52.07±5.47)和(58.61±6.11)mm]和心率[(80.47±8.22)和(90.55±6.45)次/分]改善明显,BNP[(456.36±5.24)和(684.80±6.35)ng/L]、ET[(45.77±5.22)和(66.03±5.76)ng/L]和β-内啡肽[(123.79±10.35)和(140.82±11.64)ng/L]水平降低,差异均有统计学意义($P<0.05$)。与呋塞米组比较,托伐普坦组总有效率[90.48%(38/42)和78.57%(33/42)]升高,差异有统计学意义($\chi^2=5.422$,$P=0.020$)。2组患者不良反应发生率[4.76%(2/42)和9.52%(4/42)]比较,差异无统计学意义($P>0.05$)。**结论** 托伐普坦用于老年心力衰竭患者可增强心功能,降低神经内分泌因子水平。

【关键词】 老年人;心力衰竭;神经分泌系统;托伐普坦
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Effects of tolvaptan on cardiac function and neuroendocrine factors in elderly patients with heart failure

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【Abstract】 Objective To determine the effect of tolvaptan on cardiac function and neuroendocrine factors. **Methods** A total of 84 elderly patients with heart failure (HF) admitted in Shaanxi People's Hospital from January 2017 to January 2019 were retrospectively collected in this study. According to the diuretic drugs, they were divided into furosemide group and tolvaptan group ($n=42$). After 2 weeks of treatment, the cardiac function indicators and the levels of brain natriuretic peptide (BNP), endothelin (ET) and beta-endorphin were compared between the 2 groups. SPSS statistics 18.0 was used to analyze the data. Student's t test or Chi-square test was employed for intergroup comparison. **Results** After treatment, left ventricular ejection fraction (LVEF) and 6-minute walking distance were increased, while left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), heart rate, and serum levels of BNP, ET and beta-endorphin were decreased in both groups. After treatment, the levels of LVEF [(45.77±3.41)% *vs* (40.82±4.09)%], 6-minute walking distance [(474.51±8.45) *vs* (395.90±6.48) m], LVESD [(41.09±3.47) *vs* (45.63±4.55) mm], LVEDD [(52.07±5.47) *vs* (58.61±6.11) mm] and heart rate [(80.47±8.22) *vs* (90.55±6.45) beats/min] were greatly improved, and the levels of BNP [(456.36±5.24) *vs* (684.80±6.35) ng/L], ET [(45.77±5.22) *vs* (66.03±5.76) ng/L] and beta-endorphin [(123.79±10.35) *vs* (140.82±11.64) ng/L] were notably decreased in the tolvaptan group than in the furosemide group ($P<0.05$). Compared with the furosemide group, the total effective rate of tolvaptan group was higher in tolvaptan group [90.48%(38/42) *vs* 78.57%(33/42), $\chi^2=5.422$, $P=0.020$], but no such difference was seen

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in the incidence of adverse reactions between the 2 group [(4.76%(2/42) *vs* 9.52%(4/42), $P>0.05$]. **Conclusion** Tolvaptan can improve cardiac function and reduce neuroendocrine factors in elderly patients with heart failure.

【**Key words**】 aged; heart failure; neuroendocrine system; tolvaptan

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心力衰竭是指心脏收缩和舒张功能异常,使得静脉血液淤积,动脉血液灌注不足,最终造成心脏循环功能障碍。患者临床表现为呼吸困难、全身乏力、水肿等,随着疾病进展,症状加重,严重者可能出现心源性休克,危及生命[1,2]。研究表明神经内分泌因子激活在心力衰竭发生及发展中具有重要意义,心力衰竭患者常伴心排血量降低、室壁应力提高等现象,它们也是促进神经内分泌因子激活的重要因素,一旦激活后可对心力衰竭发挥代偿作用,同时抑制心功能,导致心室重构或心肌肥厚,加重病情,因此神经内分泌因子水平的改善在疾病恢复中至关重要[3]。临床常采取药物进行治疗,既往常规治疗以呋塞米为主,虽能够有效缓解相关症状,但效果并不理想,常规利尿剂极易降低血钾、血钠浓度,并激活神经内分泌因子,导致机体对利尿剂的反应性降低,甚至可能加重水钠潴留。随着医疗水平的完善和发展,研究发现托伐普坦效果更好,其属于新型利尿剂,可有效改善心脏前后负荷,增加排尿量,减轻相关症状,但不会引起血钾、血钠丢失[4,5],为此本研究探讨了托伐普坦对心功能和神经内分泌因子的影响。

1 对象与方法

1.1 研究对象

回顾性分析2017年1月至2019年1月陕西省人民医院心血管内科老年心力衰竭患者84例,根据利尿剂药物不同分为呋塞米组和托伐普坦组,每组42例。纳入标准:(1)符合《慢性心力衰竭诊断治疗指南》中疾病诊断标准[6];(2)患者及家属同意;(3)资料齐全,意识正常,能够顺利完成研究。排除标准[7]:(1)肝肾疾病、心肌炎、器官功能异常、急性心肌梗死和恶性肿瘤;(2)研究前实施心脏手术;(3)精神疾病、文盲或沟通障碍。

1.2 方法

托伐普坦组患者在心力衰竭常规治疗基础上服用托伐普坦(浙江大冢制药有限公司,国药准字H20110115,15 mg),15 mg/次,1次/d,口服。呋塞米组患者在心力衰竭常规治疗基础上静注呋塞米(天津金耀集团湖北天药药业股份有限公司,国药准字H12020527,2 ml,20 mg),20 mg/次,1次/d。均持续用药2周。

1.3 监测指标

1.3.1 心功能指标 选择彩色多普勒二维超声显像仪及S4探头,实施心脏超声探查,检测其左心室射血分数(left ventricular ejection fraction,LVEF)、左心室收缩末期内径(left ventricular end-systolic dimension,LVESD)、左心室舒张末期内径(left ventricular end-diastolic dimension,LVEDD),同时测定静息状态下1 min的心率(heart rate,HR)及6 min步行距离,并监测高钠血症、心律失常及胃肠不适等不良反应。

总有效率:治疗后相关症状消退,心功能等级改善>2级为显效;治疗后相关症状减轻,心功能等级改善>1级为有效;治疗后未达到以上标准为无效。总有效率=(显效+有效)/42×100%[8]。

1.3.2 神经内分泌因子 密切关注治疗后2组患者病情变化并评估疗效,分别于治疗前后检测脑钠肽(brain natriuretic peptide,BNP)、内皮素(endothelin,ET)和β-内啡肽。清晨收集患者空腹静脉血5 ml,3 000转/min离心10 min,取血浆置于-80℃冰箱中待检。分别选择配套试剂盒,严格遵照说明书进行检测。

1.4 统计学处理

应用SPSS 18.0统计软件对数据进行分析。计量资料用均数±标准差($\bar{x}\pm s$)表示,组间比较采用t检验。计数资料用例数(百分率)表示,组间比较用χ^2检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 2组患者基线资料比较

托伐普坦组患者男性23例,女性19例,年龄47~76(60.2±2.6)岁,病程2~15(10.9±1.1)年,心功能分级Ⅲ级27例,Ⅳ级15例。呋塞米组患者男性22例,女性20例,年龄45~75(60.9±2.1)岁,病程2~14(11.1±1.0)年,心功能分级Ⅲ级25例,Ⅳ级17例。2组患者基线资料比较差异无统计学意义($P>0.05$)。

2.2 2组患者心功能指标比较

2组患者治疗前LVEF、LVESD、LVEDD、HR及6 min步行距离差异无统计学意义($P>0.05$)。与治疗前相比,2组患者治疗后LVEF和6 min步行距离

水平增高,LVESD、LVEDD 和 HR 水平降低,且托伐普坦组优于呋塞米组,差异均有统计学意义($P<0.05$;表 1)。托伐普坦组总有效率明显高于呋塞米组[90.48%(38/42)和 78.57%(33/42)],差异有统计学意义($\chi^2=5.422$,$P=0.020$)。

2.3 2 组患者神经内分泌因子水平比较

2 组患者治疗前 BNP、ET 及 β-内啡肽水平差异无统计学意义($P>0.05$)。与治疗前相比,2 组患者治疗后 BNP、ET 及 β-内啡肽水平降低,且托伐普坦组优于呋塞米组,差异均有统计学意义($P<0.05$;表 2)。

2.4 2 组患者不良反应发生率比较

托伐普坦组患者高钠血症 1 例,胃肠道不适 1 例,不良反应发生率 4.76%(2/42);呋塞米组患者心律失常 2 例,胃肠道不适 2 例,不良反应发生率 9.52%(4/42)。2 组患者不良反应发生率差异无统计学意义($P>0.05$)。

3 讨 论

近几年我国心力衰竭患病率逐年升高,已成为老年人死亡的主要病因[9,10]。老年患者自身基础疾病较多,各器官功能明显衰退,部分泵血能力丧失,临床表现也缺乏特异性,因此诊疗难度增加,疾病发展使得病情逐渐加重。尽早给予有效利尿药物,可改善水钠潴留现象,促进病情稳定。但心力衰竭患者常伴中心静脉压升高、代偿性肾小管肥大等现象,易导致肾小球滤过率降低甚至产生利尿剂抵抗,长期使用利尿剂还可造成电解质紊乱,增加室性心动过速及脑水肿的发生概率,因此如何选择利尿药物对保障患者安全具有重要意义[11-13]。

临床常采用呋塞米治疗,此药物静注后受肾小球滤过影响较小,同时可促进血管紧张素活性,但长期单一使用可引发高尿酸血症,不利于病情快速康复[14,15]。而托伐普坦属选择性血管加压素 V2 受体拮抗剂,可抑制精氨酸血管加压素诱导的肾集合管对水的重吸收,从而有效提高患者尿液量,增加无电解质自由水的排泄,改善心脏前负荷及心肌做功,对血钾和血钠代谢的影响也较小,可减少电解质紊乱现象的发生[16-18]。托伐普坦还可快速减轻低灌注或肾淤血造成的肾损伤,提高肾脏对利尿剂的反应,因此效果更显著[19]。本研究结果显示托伐普坦组患者总有效率 90.48%,明显高于呋塞米组 78.57%,差异具有统计学意义($P<0.05$)。

心力衰竭患者常伴神经激素调节异常,神经内分泌因子水平均不同程度升高。BNP 由心肌细胞合成,可舒张血管,心肌受损、心室负荷过重或缺血缺氧可导致 BNP 水平明显升高。ET 可促进血管收缩,心力衰竭、心肌组织缺血缺氧时,大量 ET 被合成并释放入血,参与疾病的进程[20,21]。β-内啡肽可与心血管系统受体结合,刺激心脏 k 受体,防止正常状态下心肌收缩,同时拮抗 β-肾上腺受体激活造成的心肌兴奋[22,23]。呋塞米虽可加快排尿,但同时激活交感神经和肾素-血管紧张素-醛固酮系统,促进神经内分泌因子的合成。而托伐普坦抑制神经内分泌

表 1 2 组患者治疗前后心功能指标比较

Table 1 Comparison of cardiac function indicators before and after treatment between two group ($n=42$, $\bar{x}\pm s$)

Group	LVEF (%)	LVESD (mm)	LVEDD (mm)	HR (beats/min)	6 min walking distance (m)
Tolvaptan					
Before treatment	33.58±5.10	50.86±6.78	60.87±5.98	102.36±8.47	359.62±10.25
After treatment	45.77±3.41*#	41.09±3.47*#	52.07±5.47*#	80.47±8.22*#	474.51±8.45*#
Furosemide					
Before treatment	33.90±5.33	51.14±6.92	61.51±6.30	104.05±8.56	362.07±10.92
After treatment	40.82±4.09*	45.63±4.55*	58.61±6.11*	90.55±6.45*	395.90±6.48*

LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic dimension; LVEDD: left ventricular end-diastolic dimension; HR: heart rate. Compared with before treatment, *$P<0.05$; compared with furosemide group, #$P<0.05$.

表 2 2 组患者治疗前后神经内分泌因子水平比较

Table 2 Comparison of neuroendocrine factors before and after treatment between two groups ($n=42$, ng/L, $\bar{x}\pm s$)

Group	BNP		ET		Beta-endorphin	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Tolvaptan	853.25±7.46	456.36±5.24*#	80.96±9.45	45.77±5.22*#	150.63±8.47	123.79±10.35*#
Furosemide	851.09±7.52	684.80±6.35*	81.04±9.13	66.03±5.76*	151.42±8.70	140.82±11.64*

BNP: brain natriuretic peptide; ET: endothelin. Compared with before treatment, *$P<0.05$; compared with furosemide group, #$P<0.05$.

因子的合成,可抵消常规利尿剂的负作用。本研究结果也表明托伐普坦组患者BNP、ET及β-内啡肽水平降低优于呋塞米组患者。另外,托伐普坦还可改善心功能,本研究结果也表明托伐普坦组患者治疗后相比治疗前LVEF和6 min步行距离水平增高,LVESD、LVEDD和HR水平降低,且优于呋塞米组,证实了托伐普坦的疗效,与劳荣海[24]的研究结果一致。

心力衰竭患者用药期间应关注血钠浓度变化,并根据情况及时调整剂量。本研究结果显示托伐普坦组不良反应发生率4.76%,与呋塞米组患者9.52%相比差异无统计学意义($P>0.05$),提示托伐普坦并不会产生严重不良反应,患者耐受性较好。本研究也存在一定局限性。病例数较少,患者用药时间较短,仍有待后期增加样本量继续探讨。综上所述,托伐普坦可增强心功能,改善神经内分泌因子水平,安全性高,可用于老年心力衰竭患者。

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