·临床研究·

马来酸桂哌齐特与尼莫地平治疗蛛网膜下隙出血后脑血管痉挛疗效对比研究

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【摘要】 通过经颅多普勒超声观察马来酸桂哌齐特(320 mg/d)和尼莫地平(30 mg/d)治疗前后创伤性蛛网膜下隙出血所致脑血管痉挛患者大脑中动脉血流动力学变化。结果显示,与治疗前相比,两组患者治疗第3和7天时大脑中动脉血流速度[第3天:(131.03±15.03) cm/s对(135.93±12.94) cm/s;第7天:(118.90±13.84) cm/s对(121.78±14.19) cm/s]下降(均$P=0.000$),但组间差异无统计学意义(均$P>0.05$)。两组患者治疗总有效率和药物不良反应发生率比较,差异均无统计学意义($P>0.05$)。提示马来酸桂哌齐特可以替代尼莫地平治疗蛛网膜下隙出血后脑血管痉挛。

【关键词】 马来酸盐类; 尼莫地平; 蛛网膜下腔出血,创伤性; 脑血管痉挛,颅内

The curative effect of cinepazide maleate and nimodipine in the treatment of cerebral vasospasm after subarachnoid hemorrhage

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【Abstract】 The curative effect of cinepazide maleate (320 mg/d) and nimodipine (30 mg/d) on the cerebral vasospasm caused by post-traumatic subarachnoid hemorrhage was compared. Transcranial Doppler ultrasound (TCD) was used to examine the changes of hemodynamics of middle cerebral artery (MCA) before and after treatment. On the 3rd day after treatment the blood flow velocity of MCA in both groups decreased obviously, and the difference between that in pre- and post-treatment was statistically significant (cinepazide maleate group $t=4.364$, $P=0.000$; nimodipine group $t=7.486$, $P=0.000$), but there was no statistically significant difference between 2 groups ($P=0.124$). On the 7th day, the blood flow velocity of 2 groups continously declined (cinepazide maleate group $t=5.793$, $P=0.000$; nimodipine group $t=10.364$, $P=0.000$), but there was no significant difference between 2 groups ($P=0.364$). No statistically significant difference on total effective rate and adverse drug reaction rate was seen between 2 groups ($P>0.05$). It was suggested that cinepazide maleate can replace nimodipine in the treatment for cerebral vasospasm after subarachnoid hemorrhage.

【Key words】 Maleates; Nimodipine; Subarachnoid hemorrhage, traumatic; Vasospasm, intracranial

蛛网膜下隙出血后的脑血管痉挛发病率高达30%~90%,可造成脑组织供血减少,缺血、缺氧甚至继发缺血性卒中[1-2],导致病死或病残[3]。尼莫地平是经典的防治脑血管痉挛药物[4],但有研究显示尼莫地平并无明显的脑保护作用[5],且可引起颅内再出血和颅内压改变。因此,寻找一种更适用于脑血管痉挛的治疗药物即显得尤为重要。在本研究中,我们对马来酸桂哌齐特和尼莫地平治疗颅脑创伤性蛛网膜下隙出血后脑血管痉挛的疗效进行对比分析,以观察马来酸桂哌齐特预防或治疗脑血管痉挛的效果。

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资料与方法

一、一般资料

1.纳入与排除标准 (1)脑血管痉挛诊断标准为[6]:意识障碍呈波动性(嗜睡或昏睡)、神经系统定位体征时隐时现、不明原因高热、腰椎穿刺脑脊液

表1 两组患者一般资料的比较

Table 1. Comparison of general data between 2 groups

Observation item	Nimodipine (N = 42)	Cinepazide (N = 42)	χ^2 or t value	P value
Sex case (%)			0.057	0.81
Male	30 (71.43)	29 (69.05)		
Female	12 (28.57)	13 (30.95)		
Age ($\bar{x} \pm s$, year)	32.99 ± 2.10	32.34 ± 2.11	1.328	0.547
Duration ($\bar{x} \pm s$, month)	8.47 ± 2.53	8.32 ± 2.41	2.852	0.861
GCS ($\bar{x} \pm s$, score)	6.48 ± 1.39	6.52 ± 1.47	2.235	0.712
NIHSS ($\bar{x} \pm s$, score)	9.11 ± 2.44	8.97 ± 2.21	2.563	0.745
First symptom case (%)			0.895	0.925
Headache	21 (50.00)	19 (45.24)		
Dizziness	13 (30.95)	14 (33.33)		
Concurrence	5 (11.90)	6 (14.29)		
Numbness of limbs	1 (2.38)	2 (4.76)		
Others	2 (4.76)	1 (2.38)		

GCS, Glasgow Coma Scale, Glasgow 昏迷量表; NIHSS, National Institute of Health Stroke Scale, 美国国立卫生研究院卒中量表

检查无血性液体，具备前3项中任一项且同时符合最后一项即可明确诊断。(2)有颅脑创伤史。(3)入院时Glasgow昏迷量表(GCS)评分 ≥ 5分、美国国立卫生研究院卒中量表(NIHSS)评分 ≥ 7.50分。(4)排除严重心脑血管疾病、糖尿病等可能影响疗效的因素，并排除妊娠期或可能妊娠患者。

2. 观察对象 选择2009年3月–2012年4月在辽宁省辽河油田总医院神经内科诊断与治疗的蛛网膜下隙出血后脑血管痉挛患者138例，其中84例符合本研究纳入标准，男性52例，女性32例；年龄16～71岁，平均32.56岁。采用完全随机分组方法分为马来酸桂哌齐特组和尼莫地平组。(1)马来酸桂哌齐特组：42例患者，男性29例，女性13例；年龄16～72岁，平均(32.34 ± 2.11)岁；病程3.17个月至2.33年，平均(8.32 ± 2.41)个月。主要表现为头痛(19例)、头晕(14例)或头痛头晕并存(6例)、肢体麻木(2例)。(2)尼莫地平组：42例患者，男性30例，女性12例；年龄18～71岁，平均(32.99 ± 2.10)岁；病程3.41个月至2.32年，平均(8.47 ± 2.53)个月。以头痛(21例)、头晕(13例)或头痛头晕并存(5例)、肢体麻木(1例)为首发症状。两组患者性别、年龄及症状与体征构成比等资料比较，差异无统计学意义(均$P > 0.05$，表1)，均衡可比。

二、治疗方法

1. 药品来源 马来酸桂哌齐特注射液(批号：20090105；规格：320 mg/支)由北京四环制药有限公司提供。尼莫地平(尼莫同)注射液为德国Bayer公司产品(批号：H20023730；规格：10 mg/50 ml)。

2. 给药方法 (1)马来酸桂哌齐特组：320 mg加入500 ml氯化钠溶液中静脉滴注(1次/d)，初始剂量2 mg/h，连续治疗7 d。(2)尼莫地平组：30 mg加入300 ml氯化钠溶液中静脉滴注，初始剂量1 mg/h，连续治疗7 d。两组患者静脉给药速度均根据当时血压及症状变化酌情调整滴速。

3. 疗效评价 (1)评价方法：分别于治疗后第3和7天采用经颅多普勒超声(TCD)检测患者大脑中动脉(MCA)平均血流速度，检测深度为45～60 mm，血流速度120～140 cm/s为轻度痉挛；141～200 cm/s为中度痉挛；> 200 cm/s为重度痉挛[7]。(2)疗效评价标准[6]：显效，脑血管痉挛完全解除，大脑中动脉血流速度恢复至正常值范围(约为62 cm/s)，临床症状与体征完全消失；有效，血流速度与治疗前比较有所下降，未达到痉挛程度，临床症状明显改善；无效，脑血管痉挛症状未解除，大脑中动脉血流速度与治疗前比较基本无变化，临床症状无明显改善。治疗总有效率(%) =(显效例数 + 有效例数)/总例数 × 100%。

三、统计分析方法

采用SPSS 17.0统计软件进行数据计算与分析。计量资料以均数 ± 标准差($\bar{x} \pm s$)表示，行两独立样本的t检验；治疗前后大脑中动脉血流速度的比较采用重复测量设计的方差分析，两两比较行LSD-t检验。计数资料以相对数构成比(%)或率(%)表示，采用四格表χ^2检验；两组药物不良反应发生率的比较行Fisher确切概率法。以$P \leq 0.05$为差异具有统计学意义。

结 果

表2，3结果显示，两组患者于药物治疗第3天时症状开始好转，以头痛症状缓解明显，马来酸桂哌齐特组治疗总有效率为59.52%(25/42)，高于尼莫地平组的54.76%(23/42)，但差异无统计学意义($\chi^2 = 0.194$，$P = 0.659$)；治疗第7天时，马来酸桂哌齐特组治疗总有效率为71.43%(30/42)、尼莫地平组为69.05%(29/42)，差异亦无统计学意义($\chi^2 = 0.057$，$P = 0.811$)。

由表4，5可见，治疗第3天时两组患者大脑中动脉血流速度明显减慢，与治疗前比较差异有统计

表2 两组患者治疗第3天时总有效率的比较* 例(%)

Table 2. Comparison of total effective rate on the 3rd day after treatment between 2 groups* case (%)

Group	N	Headache	Dizziness	Concurrence	Numbness of limbs	Others	Total
Nimodipine	42	13 (30.95)	8 (19.05)	2 (4.76)	0 (0.00)	0 (0.00)	23 (54.76)
Cinepazide	42	14 (33.33)	8 (19.05)	3 (7.14)	0 (0.00)	0 (0.00)	25 (59.52)

*$\chi^2 = 0.194$, $P = 0.659$

表3 两组患者治疗第7天时总有效率的比较* 例(%)

Table 3. Comparison of total effective rate on the 7th day after treatment between 2 groups* case (%)

Group	N	Headache	Dizziness	Concurrence	Numbness of limbs	Others	Total
Nimodipine	42	17 (40.48)	8 (19.05)	2 (4.76)	1 (2.38)	1 (2.38)	29 (69.05)
Cinepazide	42	15 (35.71)	10 (23.81)	4 (9.52)	1 (2.38)	0 (0.00)	30 (71.43)

*$\chi^2 = 0.057$, $P = 0.811$

表4 两组患者治疗前后大脑中动脉血流速度的比较($\bar{x} \pm s$, cm/s)

Table 4. Comparison of arterial blood flow velocity in 2 groups between before and after treatment ($\bar{x} \pm s$, cm/s)

Group	N	Pretherapy	3 d	7 d
Nimodipine	40	167.68 ± 18.29	135.93 ± 12.94	121.78 ± 14.19
Cinepazide	39	166.03 ± 18.38	131.03 ± 15.03	118.90 ± 13.84

表5 两组患者治疗前后大脑中动脉血流速度的重复测量设计的方差分析表

Table 5. The ANOVA for repeated measurement of MCA blood flow velocity before and after treatment in 2 groups

Source	*SS*	df	*MS*	*F* value	*P* value
Group	584.867	1.000	584.867	1.066	0.305
Time	90 837.770	1.622	55 997.965	504.740	0.000
Group × time	106.361	1.622	65.567	0.591	0.521
Error (group)	42 258.424	77.000	548.811		
Error (time)	13 857.639	124.906	110.944		

学意义(马来酸桂哌齐特组:$t = 4.364$, $P = 0.000$;尼莫地平组:$t = 7.486$, $P = 0.000$),但两组之间差异无统计学意义($P = 0.124$);治疗第7天时两组患者大脑中动脉血流速度持续下降,与治疗前比较差异有统计学意义(马来酸桂哌齐特组:$t = 5.793$, $P = 0.000$;尼莫地平组:$t = 10.364$, $P = 0.000$),但两组之间差异无统计学意义($P = 0.364$)。

两组患者治疗过程中无一例出现重要脏器损害,主要药物不良反应为血压下降(马来酸桂哌齐特组3例、尼莫地平组2例)和恶心(两组各1例),均经调整药物滴速后缓解,无一例停药。两组患者药物不良反应发生率比较,差异无统计学意义(Fisher确切概率法:$P = 0.841$)。

讨 论

马来酸桂哌齐特为新一代哌嗪类药物,具有腺苷增效、扩张血管和改善血流动力学作用[8],广泛应用于心脑血管疾病的治疗[9-11]。该药抗脑血管痉挛机制主要通过阻断钙离子进入血管平滑肌细胞,提高组织内腺苷和环磷腺苷水平,以达到扩张相应血管之目的。与此同时,马来酸桂哌齐特还具有抑制血小板聚集的作用,从而降低血液黏稠度、改善微循环灌注[12],可能亦是该药改善脑血管痉挛的机制之一。尼莫地平为传统抗脑血管痉挛药物,其药理学机制是通过抑制钙离子内流,加强线粒体、内质网摄取钙离子的能力,从而达到缓解痉挛目的,大多数临床研究均以尼莫地平作为对照药物[13-15]。

在本研究中,治疗第3天时马来酸桂哌齐特组和尼莫地平组患者大脑中动脉血流速度均明显下降,与治疗前比较有统计学意义,但组间差异无统计学意义;治疗第7天时两组患者大脑中动脉血流速度持续降低,与治疗前比较差异亦有统计学意义,但两组比较差异无统计学意义。治疗第3和7天时,马来酸桂哌齐特治疗效果均优于尼莫地平,但两种药物治疗总有效率差异无统计学意义。两组患者主要药物不良反应为血压下降和恶心,经调整药物滴速后症状缓解,无一例因上述不良反应停药,亦未出现重要脏器损害,表明马来酸桂哌齐特320 mg/d剂量相对安全。与尼莫地平相比,马来酸桂哌齐特能够抑制腺苷代谢,提高内源性腺苷水平和有效作用时间,具有脑保护作用[16],此为尼莫地平所不具备的优点,而在疗效、药物不良反应及药品价格上,二者无明显差异。本研究结果提示:马来酸桂哌齐特可以替代尼莫地平治疗蛛网膜下隙出血所致脑血管痉挛。

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Venue: Vancouver Convention Center, Vancouver, Canada

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The 29th CINP World Congress will be held in June 22–26, 2014 in Vancouver, Canada. The main purpose of this CINP World Congress is to provide a truly outstanding scientific and educational program featuring leading figures from around the world who are literally changing the face of neuropsychopharmacology.

The Plenary Speakers will include nobel laureates, and other innovators who are transforming our ability to visualize and manipulate the brain with a specificity that was undreamed just a few years ago. Medical practice will be informed by leading clinical researchers who are spearheading new treatment regimens for brain disorders where sensory-motor disturbance and cognitive (emotional) difficulties often reflect two sides of the same coin. These memorable lectures will be complimented by 36 Symposia spanning the broad spectrum of neuropsychopharmacolgy from both preclinical and clinical perspectives.

Scientific and educational Workshops will provide interactive discussions on the latest techniques along with opportunities to learn firsthand about new and successful clinical approaches to mental ill-health. Lively Pro and Con Debates will ensure that different perspectives are given the respect they deserve.