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扑热息痛与布洛芬对早产动脉导管未闭患儿脑氧合和脑血流速度的影响比较

张云朝, 潘娜娜

【摘要】 目的 比较扑热息痛与布洛芬对早产动脉导管未闭(PDA)患儿脑氧合和脑血流速度的影响。**方法** 选取2017年1月—2018年1月泰山医学院附属聊城市第二人民医院新生儿重症监护室收治的早产PDA患儿24例,根据治疗方法分为扑热息痛组和布洛芬组,每组12例。布洛芬组患儿给予布洛芬注射液治疗,扑热息痛组患儿给予扑热息痛注射液治疗;两组患儿均连续治疗3 d。比较两组患儿治疗5 d后PDA关闭情况,用药前30 min(T₀)及用药(60±20) min(T₁)、(180±30) min(T₂)、(360±30) min(T₃)局部脑氧饱和度(rSO₂)及局部脑组织氧摄取率(FTOE),治疗前及治疗5 d后胼胝体周围动脉平均流速、阻力指数(RI),并观察两组患儿治疗期间不良反应发生情况。**结果** (1)两组患儿治疗5 d后PDA关闭率比较,差异无统计学意义($P>0.05$)。(2)时间与方法在rSO₂、FTOE上不存在交互作用($P>0.05$);时间、方法在rSO₂、FTOE上主效应不显著($P>0.05$)。(3)两组患儿治疗前胼胝体周围动脉平均流速、RI及治疗后5 d胼胝体周围动脉平均流速比较,差异无统计学意义($P>0.05$);治疗5 d后扑热息痛组患儿胼胝体周围动脉RI高于布洛芬组($P<0.05$)。(4)两组患儿治疗期间均未发生明显不良反应。**结论** 扑热息痛与布洛芬对早产PDA患儿的PDA关闭效果相似,均不会影响患儿脑氧合和脑血流速度且安全性较高,而与扑热息痛比较,布洛芬可更有效地降低早产PDA患儿脑血流阻力。

【关键词】 动脉导管未闭; 婴儿, 早产; 扑热息痛; 布洛芬; 脑氧合; 血流速度

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252601 山东省临清市, 泰山医学院附属聊城市第二人民医院

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Impact on Cerebral Oxygenation and Cerebral Blood Flow Velocity in Premature Infants with Patent Ductus Arteriosus: a Comparison between Paracetamol and Ibuprofen

ZHANG Yunchao, PAN Nana

The Second People's Hospital of Liaocheng, Affiliated to Taishan Medical College, Linqing 252601, China

【Abstract】 Objective To compare the impact on cerebral oxygenation and cerebral blood flow velocity in premature infants with patent ductus arteriosus (PDA) between paracetamol and ibuprofen. **Methods** From January 2017 to January 2018, a total of 24 premature infants with PDA were selected from NICU, the Second People's Hospital of Liaocheng, Affiliated to Taishan Medical College, and they were divided into paracetamol group and ibuprofen group according to therapeutic methods, with 12 cases in each group. Premature infants in ibuprofen group were given ibuprofen injection, while premature infants in paracetamol group were given paracetamol injection; both groups were continuously treated for 3 days. Closure rate of PDA 5 days after treatment, rSO_2 and FTOE 30 minutes before drug use (T_0), (60 ± 20) minutes (T_1), (180 ± 30) minutes (T_2) and (360 ± 30) minutes (T_3) after drug use, mean velocity and RI of pericallosum arteries before treatment and 5 days after treatment were compared between the two groups, and incidence of adverse reactions was observed during treatment. **Results** (1) There was no statistically significant difference in closure rate of PDA 5 days after treatment between the two groups ($P > 0.05$). (2) There was no statistically significant interaction between time and method in rSO_2 or FTOE ($P > 0.05$); main effects of time and method were not statistically significant in rSO_2 or FTOE ($P > 0.05$). (3) There was no statistically significant difference in mean velocity and RI of pericallosum arteries before treatment between the two groups ($P > 0.05$); 5 days after treatment, RI of pericallosum arteries in paracetamol group was statistically significantly higher than that in ibuprofen group ($P < 0.05$), while no statistically significant difference of mean velocity of pericallosum arteries was found between the two groups ($P > 0.05$). (4) No one in the two groups occurred any obvious adverse reactions during treatment. **Conclusion** Paracetamol and ibuprofen have similar closure effect of PDA and safety in treating premature infants with PDA, but compared with paracetamol, ibuprofen can more effectively reduce the cerebral blood flow resistance.

【Key words】 Ductus arteriosus, patent; Infant, premature; Paracetamol; Ibuprofen; Cerebral oxygenation; Blood flow velocity

动脉导管未闭(PDA)是呼吸窘迫综合征(RDS)早产儿的常见并发症,有60%~70%胎龄<28周的早产儿接受PDA内科或外科治疗^[1]。研究表明,动脉导管水平左向右分流合并RDS的新生儿易出现呼吸衰竭、颅内出血、支气管肺发育不良和坏死性小肠结肠炎等^[2],因此,动脉导管水平发生明显左向右分流之前建议关闭PDA。非甾体类抗炎药环氧化酶抑制剂吲哚美辛或布洛芬可使70%~80%的PDA患儿动脉导管永久性关闭^[3],但吲哚美辛会引起严重胃肠道反应和肾损伤,而布洛芬的不良反应相对较小,被认为是治疗PDA的首选药物^[4]。目前,吲哚美辛与布洛芬对婴幼儿脑氧合和脑血流速度的影响尚存在争议^[5-7],且早产儿PDA的具体发病尚不清楚。研究发现,扑热息痛与吲哚美辛和布洛芬的作用相似,但安全性较高,且既往研究中也未有服用扑热息痛后不良反应的研究报道^[6, 8-11]。本研究旨在比较扑热息痛与布洛芬对早产PDA患儿脑氧合和脑血流速度的影响,现报道如下。

1 资料与方法

1.1 一般资料 选取2017年1月—2018年1月泰山医学院附属聊城市第二人民医院新生儿重症监护室收治的早产PDA患儿24例,胎龄<32周。纳入标准:(1)发病时间为24~72 h者;(2)需呼吸支持者;(3)超声心动图检查结果显示左心房直径与主动脉根部直径比率>1.3或动脉导管>1.5 mm的左向右分流者^[12]。排除标准:(1)伴有先天性畸形者;(2)伴有危及生命的感染或水肿者;(3)伴有持续肺动脉高压(PPH)者;(4)伴有3、4级脑室内出血者;(5)行心血

管支持及使用儿茶酚胺等影响脑血流的药物者。根据治疗方法将所有患儿分为扑热息痛组和布洛芬组,每组12例。两组患儿胎龄、出生体质量、男性比例、产前类固醇使用率、剖宫产者所占比例、脐静脉血pH值、吸入氧浓度(FiO_2)、表面活性剂使用率、机械通气者所占比例、出生时间、PDA直径、左心房内径/升主动脉内径比值、住院时间及脓毒症、支气管肺发育不良、坏死性小肠结肠炎、脑室内出血者所占比例比较,差异无统计学意义($P > 0.05$,见表1),具有可比性。本研究经泰山医学院附属聊城市第二人民医院医学伦理委员会审核批准,所有患儿父母对本研究知情同意。

1.2 方法 布洛芬组患儿给予布洛芬注射液(南京艾德凯腾生物医药有限责任公司生产,生产批号:20101101)10 mg/kg,静脉注射,分别于首次注射24 h、48 h后给予5 mg/kg。扑热息痛组患儿给予扑热息痛注射液(由吉林百年汉克制药有限公司生产,批准文号H20053989)15 mg/kg,静脉注射,1次/6 h。两组患儿均连续治疗3 d。

1.3 观察指标

1.3.1 PDA关闭情况 记录治疗5 d后两组患儿PDA关闭情况。

1.3.2 脑氧合 分别于用药前30 min (T_0)和用药后(60 ± 20) min (T_1)、(180 ± 30) min (T_2)、(360 ± 30) min (T_3)采用近红外光谱技术检测两组患儿局部脑氧饱和度(rSO_2),采样间隔时间6 s,具体如下:患儿仰卧位并在安静或睡觉状态,将一个发光二极管和两个远距离传感器固定至患儿头前部区域,记录 rSO_2 ^[13];采用脉搏血氧仪检测脉搏血氧饱和度(SpO_2),

表 1 两组患儿一般资料比较
Table 1 Comparison of general information between the two groups

组别	例数	胎龄 ($\bar{x} \pm s$, 周)	出生体质量 ($\bar{x} \pm s$, g)	男性 [n (%)]	产前使用类固醇 [n (%)]	剖宫产 [n (%)]	脐静脉血 pH 值 ($\bar{x} \pm s$)	FiO ₂ ($\bar{x} \pm s$, %)	使用表面活性剂 [n (%)]
布洛芬组	12	28.2 ± 1.2	1 046 ± 291	5 (41.7)	12 (100.0)	6 (50.0)	7.30 ± 0.13	46.0 ± 2.0	11 (91.7)
扑热息痛组	12	27.8 ± 0.1	907 ± 145	8 (66.7)	8 (66.7)	9 (75.0)	7.26 ± 0.04	46.0 ± 2.3	12 (100.0)
<i>t</i> 值		-0.992	0.887	-	-	-	-0.375	-0.027	-
<i>P</i> 值		0.658	0.170	0.396	0.095	0.388	0.408	0.376	0.998

组别	机械通气 [n (%)]	出生时间 ($\bar{x} \pm s$, h)	PDA 直径 ($\bar{x} \pm s$, mm)	左心房内径 / 升主动 脉内径比值 ($\bar{x} \pm s$)	住院时间 ($\bar{x} \pm ss$, d)	脓毒症 [n (%)]	支气管肺发育不 良 [n (%)]	坏死性小肠结 肠炎 [n (%)]	脑室内出血 [n (%)]
布洛芬组	5 (41.7)	41 ± 6	1.9 ± 0.3	1.7 ± 0.3	66 ± 19	3 (25.0)	2 (16.7)	2 (16.7)	2 (16.7)
扑热息痛组	4 (33.3)	42 ± 8	1.8 ± 0.3	1.6 ± 0.5	66 ± 53	6 (50.0)	3 (25.0)	0	3 (25.0)
<i>t</i> 值	-	0.764	-1.482	-0.073	0.846	-	-	-	-
<i>P</i> 值	0.354	0.653	0.342	0.874	0.894	0.632	0.057	0.052	0.999

注: FiO₂= 吸入氧浓度, PDA= 动脉导管未闭; - 为此项数据

计算局部脑组织氧摄取率 (FTOE), FTOE = (SpO₂-rSO₂) / SpO₂ [2]。

1.3.3 脑血流速度 分别于治疗前及治疗 5 d 后采用二维多普勒超声、频谱分析仪检测两组患儿脐动脉周围动脉平均流速、阻力指数 (RI), 每个时间点连续采集 5 个最佳质量的心动周期 (速度曲线的最大振幅)。

1.3.4 不良反应 观察两组患儿治疗期间不良反应发生情况, 包括尿量 <1 ml·kg⁻¹·h⁻¹、血小板计数 <50 000/mm³ (50 × 10⁹/L)、肌酐和谷氨酸氨基转移酶 (AST) 较基线值升高 >20%、胃肠孤立穿孔出血、3~4 级脑室内出血、其他出血。

1.4 统计学方法 采用 SPSS 22.0 统计软件进行数据分析, 计量资料以 ($\bar{x} \pm s$) 表示, 组间比较采用两独立样本 *t* 检验; 重复测量资料采用双因素重复测量方差分析; 计数资料分析采用 Fisher's 确切概率法。以 *P* < 0.05 为差异有统计学意义。

2 结果

2.1 两组患儿 PDA 关闭率比较 布洛芬组患儿治疗 5 d 后 PDA 关闭 10 例, 占 83.3%; 扑热息痛组患儿治疗 5 d 后 PDA 关闭 8 例, 占 66.7%。两组患儿治疗 5 d 后 PDA 关闭率比较, 差异无统计学意义 ($\chi^2=0.889$, *P*=0.475)。

2.2 两组患儿治疗前后 rSO₂、FTOE 比较 时间与方法在 rSO₂、FTOE 上不存在交互作用 (*P* > 0.05); 时间、方法在

rSO₂、FTOE 上主效应不显著 (*P* > 0.05, 见表 2)。

2.3 两组患儿治疗前及治疗 5 d 后脑血流速度比较 两组患儿治疗前脐动脉周围动脉平均流速、RI 及治疗 5 d 后脐动脉周围动脉平均流速比较, 差异无统计学意义 (*P* > 0.05); 治疗 5 d 后扑热息痛组患儿脐动脉周围动脉 RI 高于布洛芬组, 差异有统计学意义 (*P* < 0.05, 见表 3)。

表 3 两组患儿治疗前及治疗 5 d 后脑血流速度比较 ($\bar{x} \pm s$)
Table 3 Comparison of cerebral blood flow velocity between the two groups before and 5 days after treatment

组别	例数	平均流速 (cm/s)		RI	
		治疗前	治疗 5 d 后	治疗前	治疗 5 d 后
布洛芬组	12	15.32 ± 5.42	18.62 ± 3.52	0.68 ± 0.11	0.54 ± 0.05
扑热息痛组	12	16.18 ± 3.64	16.91 ± 5.37	0.69 ± 0.02	0.67 ± 0.03
<i>t</i> 值		0.456	0.923	0.310	7.723
<i>P</i> 值		0.653	0.366	0.760	<0.01

注: RI= 阻力指数

2.4 不良反应 两组患儿治疗期间均未发生明显不良反应。

3 讨论

扑热息痛和传统的非甾体类抗炎药 (如布洛芬或吲哚美

表 2 两组患儿治疗前后 rSO₂、FTOE 比较 ($\bar{x} \pm s$)
Table 2 Comparison of rSO₂ and FTOE between the two groups before and after treatment

组别	例数	rSO ₂ (%)				FTOE			
		T0	T1	T2	T3	T0	T1	T2	T3
布洛芬组	12	72.36 ± 1.36	71.95 ± 3.99	73.45 ± 5.32	74.52 ± 1.26	0.22 ± 0.11	0.26 ± 0.14	0.20 ± 0.07	0.25 ± 0.12
扑热息痛组	12	74.14 ± 1.96	74.51 ± 4.34	72.03 ± 3.49	73.00 ± 5.11	0.20 ± 0.10	0.25 ± 0.12	0.30 ± 0.15	0.23 ± 0.13
<i>F</i> 值		<i>F</i> _{时间} =0.306, <i>F</i> _{组间} =0.213, <i>F</i> _{交互} =1.996				<i>F</i> _{时间} =0.669, <i>F</i> _{组间} =0.143, <i>F</i> _{交互} =1.305			
<i>P</i> 值		<i>P</i> _{时间} =0.821, <i>P</i> _{组间} =0.645, <i>P</i> _{交互} =0.120				<i>P</i> _{时间} =0.573, <i>P</i> _{组间} =0.706, <i>P</i> _{交互} =0.278			

注: rSO₂= 局部脑氧饱和度, FTOE= 局部脑组织氧摄取率

辛)均可通过不同机制抑制环氧合酶(COX)并降低前列腺素水平^[6, 14],且既往研究比较扑热息痛与布洛芬治疗早产PDA患儿的临床疗效发现,扑热息痛对PDA关闭率与布洛芬相似,且无不良反应发生^[8, 11]。本研究结果显示,两组患儿治疗5d后PDA关闭率比较无统计学差异,与上述研究结果一致,但具体作用机制尚不清楚。

近红外光谱技术是建立在光学原理基础上的无创检测方法,是将特定光区内的近红外光透过头皮和颅骨射入脑组织检测脑氧合,包括 rSO_2 、FTOE,其中 rSO_2 反映的是局部大脑氧饱和度^[13];FTOE反映的是氧气输送和氧气消耗之间的平衡,其增加则表明脑组织氧气利用增加,其减少表明脑组织氧气使用量低于供应^[15]。本研究结果显示,时间与方法在 rSO_2 、FTOE上不存在交互作用,时间、方法在 rSO_2 、FTOE上主效应不显著,提示扑热息痛与布洛芬对早产PDA患儿的脑氧合无影响,与ALDERLIESTEN等^[16]研究结果一致。本研究结果显示,两组患儿治疗5d后胼胝体周围动脉平均流速比较无统计学差异,扑热息痛组患儿胼胝体周围动脉RI高于布洛芬组,提示扑热息痛与布洛芬对早产PDA患儿脑血流速度无影响,但较扑热息痛,布洛芬可有效降低早产PDA患儿脑血流阻力。本研究结果还显示,两组患儿治疗期间未发生明显不良反应,提示扑热息痛与布洛芬未增加早产PDA患儿不良反应,安全性较高。

综上所述,扑热息痛与布洛芬对早产PDA患儿的PDA关闭效果相似,均不会影响患儿的脑氧合和脑血流速度且安全性较高,而与扑热息痛相比,布洛芬可更有效地降低早产PDA患儿脑血流阻力。

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