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瑞芬太尼对急性高容量血液稀释后颅内动脉瘤夹闭术患者脑氧代谢以及术后认知功能的影响

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摘要 目的:探究瑞芬太尼对急性高容量血液稀释(AHH)后颅内动脉瘤夹闭术患者脑氧代谢以及术后认知功能的影响。**方法:**选择2015年5月至2016年12月期间在我院进行颅内动脉瘤夹闭术的92例患者作为研究对象,并将其随机均分为研究组和对照组,每组46例,研究组给予瑞芬太尼治疗,对照组给予硝酸甘油治疗。对两组患者AHH前(T0)、AHH后(T1)、降压前(T2)、降压后30 min(T3)、动脉瘤夹闭术后5 min(T4)等时间点的平均动脉压(MAP)、心率(HR)进行记录,在T2-T4时间点对颈内静脉球部血、桡动脉血两处位置的动、静脉血氧饱和度(SAO₂、SjvO₂)、动脉血氧分压(PAO₂)、静脉血氧分压(PjvO₂)进行统计,计算动脉氧含量(CAO₂)、颈内静脉氧含量(CjvO₂)、动脉颈内静脉球部血氧差(Da-jvO₂)、颈内静脉球部动脉乳酸差(VADL)和脑氧摄取率(CERO₂)。在术前、术后3 d、术后7 d采用简易智力状态量表(MMSE)对两组患者的认知功能进行评估。**结果:**相对于T2时间点,在T3、T4时间点,两组患者MAP均出现显著降低(P<0.05);对照组患者HR显著升高,研究组患者HR显著降低(P<0.05)。两组患者SaO₂均为100.00%,在T3、T4时间点研究组SjvO₂、CjvO₂显著高于T2时间点,且较对照组患者升高,差异均有统计学意义(P<0.05),Da-jvO₂、CERO₂显著低于T2时间点,且较对照组患者降低,差异均有统计学意义(P<0.05)。PaO₂、CaO₂、PjvO₂、VADL组间比较差异均无统计学意义(P>0.05)。术前、术后3 d、术后7 d两组患者的MMSE评分比较均无统计学差异(P>0.05),术前、术后7 d两组患者的MMSE评分均高于术后3 d的MMSE评分(P<0.05)。**结论:**瑞芬太尼对急性高容量血液稀释进行颅内动脉瘤夹闭术,能够有效维持患者机体血流动力学稳定,同时还可以对脑氧代谢率进行有效控制,相对于硝酸甘油进行急性高容量血液稀释,瑞芬太尼优势较为明显,但对于认知功能无明显的改善作用。

关键词:急性高容量血液稀释;瑞芬太尼;脑氧代谢;认知功能;颅内动脉瘤

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Effect of Remifentanyl on Cognitive Function and Cerebral Oxygen Metabolism in Patients with Intracranial Aneurysm Clipping after Acute Hypervolemic Hemodilution

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ABSTRACT Objective: To investigate the effect of remifentanyl on the cognitive function and cerebral oxygen metabolism in patients with intracranial aneurysms after acute hypervolemic hemodilution (AHH). **Methods:** A total of 92 patients, who underwent intracranial aneurysm clipping in Suining Central Hospital from May 2015 to December 2016, were selected and were randomly divided into study group (n=46) and control group (n=46). The study group was treated with remifentanyl, and the control group was treated with nitroglycerin. Mean arterial pressure (MAP) and heart rate (HR) of the patients in the two groups before AHH (T0), after AHH (T1), before lowering blood pressure (T2), 30min after lowering blood pressure (T3), 5 min after aneurysm clipping (T4) were recorded. The arterial and venous blood oxygen saturation (SAO₂, SjvO₂), arterial oxygen partial pressure (PAO₂), and arterial oxygen partial pressure (PjvO₂) were counted at T2-T4 time points. The arterial oxygen content (CAO₂), internal jugular vein oxygen content (CjvO₂), arterial internal jugular bulb oxygen deficit (Da-jvO₂), arterial bulb lactate difference (VADL) and brain oxygen uptake rate (CERO₂) were calculated. The cognitive functions of two groups were evaluated by the Mini Mental State Scale (MMSE) before operation, 3 d and 7 d after operation. **Results:** Compared with the T2 time point, the MAP was decreased significantly in the two groups at T3 and T4 time points (P<0.05). The HR in the control group was increased significantly, but the HR in the study group was decreased significantly (P<0.05). The SaO₂ of the two groups was 100%. At T3 and T4 time points, SjvO₂ and CjvO₂ in the study group were significantly higher than those at T2 time point, which was higher than those in the control group, and the differences were statistically significant (P<0.05); the Da-jvO₂ and CERO₂ were significantly lower than at T2 time point, which were lower than those in the control group, and the differences were statistically significant (P<0.05). There were no significant differences in the PaO₂, CaO₂, PjvO₂, VADL between the two groups (P>0.05).

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There were no significant differences in MMSE scores between the two groups before operation, 3d and 7d after operation ($P>0.05$); the MMSE scores of the two groups before operation and 7d after operation were higher than those of the two groups 3d after operation ($P<0.05$). **Conclusion:** Remifentanyl in the acute hypervolemic hemodilution with intracranial aneurysm clipping can effectively maintain the stability of hemodynamics of patients, at the same time, the rate of cerebral oxygen metabolism can be effectively controlled. Compared with nitroglycerin, remifentanyl is superior in acute hypervolemic hemodilution, but there is no obvious improvement in cognitive function.

Key words: Acute hypervolemic hemodilution; Remifentanyl; Cerebral oxygen metabolism; Cognitive function; Intracranial aneurysm

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前言

颅内动脉瘤是一种常见的血管性疾病,通常表现为由局部血管异常改变而产生的脑血管瘤样突起,首发症状为自发性蛛网膜下腔出血,同时还伴有发作性头痛或神经压迫,具有较高的病死率和致残率^[1]。颅内动脉瘤夹闭术是治疗颅内动脉瘤的常用方法,但在行颅内动脉瘤夹闭手术时,麻醉诱导插管、瘤体分离、夹闭等操作易引起血压产生剧烈波动而导致患者大量出血,甚至造成动脉瘤破裂,因此在手术过程中常用控制性降压(CH)和急性高容量血液稀释(AHH)等方式以节约用血^[2]。同时临床治疗中常采用扩血管药和 β 受体阻断药作为治疗药物,瑞芬太尼是其中的药物之一,其主要发挥降血压、镇痛、降低心率(HR)等作用,能够用于控制性降压^[3,4]。既往研究^[5]关于瑞芬太尼进行CH对血流动力学的影响报道较多,但瑞芬太尼进行AHH对患者脑氧代谢及认知功能的影响相关报道较少。鉴于此,本次研究主要探讨瑞芬太尼进行AHH对行颅内动脉瘤术

患者机体内脑氧代谢以及认知功能的影响,现将本研究内容报道如下:

1 资料与方法

1.1 一般资料

选择2015年5月至2016年12月期间内在我院内进行颅内动脉瘤夹闭术的92例患者作为研究对象,并将其随机均衡分为研究组和对照组,每组46例,年龄范围35-60岁,平均年龄(48.32 ± 3.24)岁,体重45-85 kg,平均体重(59.43 ± 4.65)kg。纳入标准:患者术前Hunt-Hess(H-H)分级^[6]主要为I、II级,美国麻醉医师协会(ASA)分级主要为I、II级;红细胞比容(HCT)为35%-45%,血红蛋白(Hb) ≥ 100 g/L,白蛋白35-45 g/L。排除标准:具有严重心肺疾病患者;循环系统疾病患者;肝肾及血功能不正常患者;有药物过敏史者。研究组与对照组在年龄、体重、H-H分级、ASA分级、文化程度等方面比较无统计学差异($P>0.05$),具有可比性。

表1 两组患者基本资料比较

Table 1 Comparison of basic data of two groups

Groups	n	Gender(male / female)	Age(years)	Weight(Kg)	H-H		ASA		Degree of education	
					I	II	I	II	Primary and junior high school	High school and above
Study group	46	18/28	48.23 $\pm$ 4.57	59.72 $\pm$ 6.78	27	19	29	17	31	15
Control group	46	21/25	48.41 $\pm$ 5.63	59.63 $\pm$ 5.79	25	21	26	20	29	17
t/x ²	-	0.167	0.168	0.068	0.273		0.281		0.192	
P	-	0.683	0.867	0.946	0.618		0.594		0.662	

1.2 方法

所有研究对象在术前30 min内需要进行0.5 mg盐酸戊乙奎醚注射液肌注,手术开始后静脉开放,将心电监护仪连接在患者上。两组患者首先进行0.05 mg/kg咪达唑仑、3-4 μ g/kg芬太尼、1 mg/kg阿曲库铵和1.5-2 mg/kg丙泊酚静脉滴注诱导,再行气管插管,术中麻醉维持选择3-6 mg/(kg·H)丙泊酚和阿曲库铵0.5-0.7 mg/(kg·H)以微量泵泵入,对照组镇痛选择芬太尼间断静注,研究组患者选择6-10 μ g/(kg·H)瑞芬太尼泵入,但研究组患者瑞芬太尼停药后可能存在痛觉过敏反应,因此需要在手术完成前30 min进行0.1-0.2 mg芬太尼静脉注射。在患者行麻醉诱导后,需要在桡动脉内穿刺置管进行动脉血压的连续监测,同时在患者右侧颈内静脉内穿刺置入双腔管,左侧颈内静脉穿刺并向头侧置管12-15 cm,使管尖达到颈内静脉球部水

平,即体表投影在耳垂处,手术结束前10 min,所有麻醉药物停用。

1.3 AHH方法

由于患者在进入手术室前需要禁食禁水,因此需要先采用6-8 mL/kg复方乳酸钠对丢失体液量进行补充。手术开始时4%琥珀酰明胶以15-20 mL/(kg·H)速率静脉输注,完成后方能剪开硬脑膜,在AHH持续30 min后进行HCT检测,指标稳定在25%-32%左右时输液速率降低,采用生理盐水替代。若Hb <80 g/L, HCT $<25\%$ 时,需要异体血输注维持HCT在25%以上。开颅前患者均需250 mL 20%甘露醇滴注,硬脑膜剪开后分离、夹闭动脉瘤期间进行CH,对照组采用1-5 μ g/(kg·min)速率泵入硝酸甘油,研究组以12-30 μ g/(kg·H)速率泵入瑞芬太尼。若平均动脉压(MAP) <65 mmHg,需要将瑞芬太尼和硝酸甘油泵入

速度降低,在夹闭动脉瘤后 10 min 停止 CH。

1.4 观察指标

在手术过程中对患者收缩压(SBP)、舒张压(DBP)、MAP、HR、心电图(ECG)、血氧饱和度(SaO₂)等指标进行监测。时间点选择 AHH 前(T0)、AHH 后(T1)、降压前(T2)、降压后 30 min (T3)、动脉瘤夹闭后 5 min(T4),记录患者 MAP、HR 等相关指标,在 T2-T4 时间点分别进行血气分析,主要采集颈内静脉球部血及桡动脉血,分析指标包括静脉血氧饱和度(SjvO₂)、静脉血氧分压(PjvO₂)、动脉血氧饱和度(SaO₂)、动脉血氧分压(PaO₂、Hb 及 HCT,对患者动脉氧含量(CaO₂)、颈内静脉氧含量(CjvO₂)、动脉颈内静脉球部血氧差(Da-jvO₂)、颈内静脉球部动脉乳酸差(VADL)和脑氧摄取率(CERO₂)等指标进行计算。氧含量计算公式:CaO₂=Hb × 1.36 × SaO₂+PaO₂ × 0.0031;CjvO₂=Hb × 1.36 × SjvO₂+PjvO₂ × 0.0031;Da-jvO₂=CaO₂-CjvO₂;CERO₂=Da-jvO₂/CaO₂。在术前、术后 3 d、术后 7 d 采用简易智力状态量表(MMSE)对两组患者的认知功能进行评估,MMSE

主要从地点定向力、时间定向力、注意力及计算力、即刻记忆、延迟记忆、语言、视觉这 7 个维度进行评估,共 30 个题目,总分为 30 分,分数越高,认知功能越好。

1.5 统计分析

本研究所有数据采用 SPSS18.0 进行统计分析,计数资料采用率(%)表示,比较采用 χ^2 检验,血气指标、MMSE 评分等计量资料采用均数 $\pm$ 标准差($\bar{x} \pm s$)形式表示,各组内不同时点各指标的变化采用重复测量方差分析,组间比较采用两样本 t 检验,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 患者心血管相关指标比较

相对于 T2 时间点,在 T3、T4 时间点,两组患者 MAP 均出现显著下降($P<0.05$);对照组患者 HR 显著增加,研究组患者 HR 显著降低,且研究组 HR 低于对照组($P<0.05$)。如下表 2 所示。

表 2 患者心血管相关指标比较($\bar{x} \pm s$)

Table 2 Comparison of cardiovascular related indexes in patients($\bar{x} \pm s$)

Indexes	Groups	T0	T1	T2	T3	T4
HR(mmHg)	Control group(n=46)	78.91 $\pm$ 9.65	81.53 $\pm$ 8.79	80.81 $\pm$ 8.92	99.23 $\pm$ 3.21 ^{&}	98.32 $\pm$ 9.34 ^{&}
	Study group(n=46)	81.22 $\pm$ 8.47	79.74 $\pm$ 9.85	79.53 $\pm$ 9.43	63.45 $\pm$ 6.54 ^{&#}	64.54 $\pm$ 8.45 ^{&#}
MAP(mmHg)	Control group(n=46)	82.48 $\pm$ 9.43	84.62 $\pm$ 9.74	85.85 $\pm$ 9.48	63.63 $\pm$ 9.31 ^{&}	63.72 $\pm$ 9.67 ^{&}
	Study group(n=46)	89.74 $\pm$ 8.54	89.71 $\pm$ 9.82	86.72 $\pm$ 8.76	64.94 $\pm$ 8.59 ^{&}	63.61 $\pm$ 8.78 ^{&}

Notes: Compared with the control group, [#] $P<0.05$; compared with T2 time point, [&] $P<0.05$.

2.2 两组患者血气分析指标比较

两组患者各时间点 SaO₂ 均为 100.00%。在 T3、T4 时间点,研究组 SjvO₂、CjvO₂ 显著高于 T2 时间点,且较对照组患者升高,差异均有统计学意义($P<0.05$),Da-jvO₂、CERO₂ 显著低于

T2 时间点,且较对照组患者降低,差异均有统计学意义($P<0.05$)。PaO₂、CaO₂、PjvO₂、VADL 组间比较差异均无统计学意义($P>0.05$),如下表 3 所示。

表 3 两组患者血气分析指标比较($\bar{x} \pm s$)

Table 3 Comparison of blood gas analysis indexes between two groups($\bar{x} \pm s$)

Indexes	Groups	T2	T3	T4
PaO ₂ (mmHg)	Control group(n=46)	517.41 $\pm$ 21.34	507.71 $\pm$ 26.57	511.41 $\pm$ 16.48
	Study group(n=46)	521.65 $\pm$ 22.56	496.83 $\pm$ 24.48	508.72 $\pm$ 19.59
CaO ₂ (mmHg)	Control group(n=46)	130.83 $\pm$ 12.36	128.72 $\pm$ 15.37	126.85 $\pm$ 11.49
	Study group(n=46)	130.52 $\pm$ 13.53	129.42 $\pm$ 14.48	127.64 $\pm$ 12.32
PjvO ₂ (mmHg)	Control group(n=46)	37.57 $\pm$ 11.47	41.86 $\pm$ 13.47	39.43 $\pm$ 11.47
	Study group(n=46)	38.71 $\pm$ 12.83	39.62 $\pm$ 14.83	40.81 $\pm$ 11.59
SjvO ₂ (%)	Control group(n=46)	67.43 $\pm$ 12.42	68.31 $\pm$ 11.56	69.46 $\pm$ 11.43
	Study group(n=46)	68.82 $\pm$ 13.34	84.73 $\pm$ 12.47 ^{&#}	83.81 $\pm$ 12.36 ^{&#}
CjvO ₂ (ml/L)	Control group(n=46)	87.32 $\pm$ 11.32	87.72 $\pm$ 8.48	86.44 $\pm$ 11.36
	Study group(n=46)	88.61 $\pm$ 12.44	108.41 $\pm$ 9.46 ^{&#}	106.43 $\pm$ 10.48 ^{&#}
VADL(mmol/L)	Control group(n=46)	0.16 $\pm$ 0.12	0.14 $\pm$ 0.13	0.181 $\pm$ 0.11
	Study group(n=46)	0.16 $\pm$ 0.13	0.14 $\pm$ 0.11	0.16 $\pm$ 0.12
Da-jvO ₂ (ml/L)	Control group(n=46)	41.53 $\pm$ 12.42	40.56 $\pm$ 11.57	39.42 $\pm$ 11.29
	Study group(n=46)	42.74 $\pm$ 13.57	21.73 $\pm$ 12.68 ^{&#}	21.84 $\pm$ 12.48 ^{&#}
CERO ₂ (%)	Control group(n=46)	32.41 $\pm$ 8.47	32.22 $\pm$ 7.14	31.62 $\pm$ 9.58
	Study group(n=46)	33.62 $\pm$ 9.83	17.81 $\pm$ 8.34 ^{&#}	18.43 $\pm$ 8.87 ^{&#}

Notes: Compared with the control group [#] $P<0.05$; compared with T2 time point, [&] $P<0.05$.

2.3 两组患者 MMSE 评分比较

在术前、术后 3 d、术后 7 d 两组患者的 MMSE 评分均无统

计学差异($P>0.05$),术前、术后 7 d 两组患者的 MMSE 评分均高于术后 3 d 的 MMSE 评分($P<0.05$),如下表 4 所示。

表 4 两组患者 MMSE 评分比较($\bar{x}\pm s$,分)

Table 4 Comparison of MMSE scores between two groups($\bar{x}\pm s$, scores)

Groups	Preoperative	Postoperative 3 d	Postoperative 7 d
Control group(n=46)	26.40 $\pm$ 2.31 [#]	23.64 $\pm$ 2.24	25.87 $\pm$ 2.26 [#]
Study group(n=46)	26.03 $\pm$ 2.28 [#]	23.83 $\pm$ 2.29	25.93 $\pm$ 2.30 [#]
t	0.773	0.402	0.450
P	0.441	0.688	0.899

Note: Compared with postoperative 3 d, [#] $P<0.05$.

3 讨论

颅内动脉瘤手术治疗过程较为复杂,因此需要尽量减少手术过程中的出血量,使得手术视野清晰,动脉瘤跨壁压下降,避免在进行暴露分离动脉瘤时出现瘤体破裂^[7]。颅内动脉瘤夹闭术已普遍运用 CH,CH 时间较长易导致患者出现可脑供血不足、缺氧等症^[8]。因此在手术前行 AHH 能够使得动脉瘤跨壁压保持平稳,术前嘱患者禁水、禁食及利尿药,纠正患者脱水状态,稳定患者术中血流动力学,预防相关指标的大幅波动造成脑出血或是动脉瘤破裂等,CH 安全性提高^[9]。

本次研究采用 4%琥珀酰明胶进行 AHH 后,使得患者机体 HCT<30%,Hb<9 g/L,从而稀释血液,保证 HR、MAP 水平无显著变化。临床治疗中,夹闭颅内动脉瘤手术中 CH 药物有多种,但可能存在不良反应,如心律失常、心肌抑制、氰化物中毒、HR 增快及苏醒延迟等,需要及时处理^[10,11]。本次研究采用硝酸甘油与瑞芬太尼进行 CH,机体内硝酸甘油可转化为一氧化氮,通过一氧化氮进行扩血管,能够反射性增快 HR,若药物时间较长,易导致反跳性高血压、快速血管耐受及潜在氰化物中毒等并发症。本次研究结果显示对照组在 T3、T4 时间点 HR 显著增加。患者心动过速危害心血管系统,因为心动过速使得心肌氧耗量增加,氧供量降低。在药理学上,瑞芬太尼是一类新型超短效阿片类 μ 受体激动药,能够起到柔和降压的效果,能够无反射性的增加 HR,引起反跳性高血压^[12,13]。瑞芬太尼进行 CH 机制是^[14,15]:能够有效抑制患者中枢神经系统及自主神经;使得手术过程中儿茶酚胺类物质尤其是肾上腺素释放受到抑制;通过内皮依赖机制,前列环素、一氧化氮释放,使得血管扩张;通过非内皮依赖机制,对电压依赖性钙通道进行抑制,血管扩张。本次研究结果显示研究组患者采用瑞芬太尼,降压效果较为显著,在 T3、T4 时间点 HR 减慢较为明显,分析原因可能是阿片受体类药物能够起到兴奋迷走神经、窦房结抑制等作用^[16]。

对手术过程中脑氧代谢情况进行评价,结果显示 AHH 联合 CH 手术的安全性主要参考脑氧供需平衡进行判断,参考 Fick 原理,SjvO₂、Da-jvO₂ 能够反应脑血流相关指标及脑氧耗量间的关系,即脑氧供需平衡。采集颈静脉球部血液进行 SjvO₂ 检测,并计算 Da-jvO₂,两者是评估全脑血流代谢的重要指标。CERO₂ 能够反映组织内呼吸、组织灌注,主要是机体微循环内灌注存在关系,正常范围为 23%-32%,其代表的是脑组织氧供,VADL 则能够反映脑组织氧耗。在颈内静脉内进行逆插管,

抽取脑组织直接回流的血液,血液 VADL 指标能够反应脑组织乳酸净生成量,其正常值为(0.19 $\pm$ 0.10)mmol/L,若 VADL 大于这个范围,表明脑氧供不足,脑内无氧代谢增加。本次研究结果显示,研究组患者 SjvO₂、CjvO₂ 指标显著增加,Da-jvO₂、CERO₂ 降低;研究组患者 SjvO₂、CjvO₂、Da-jvO₂ 和 CERO₂ 指标变化并不显著,这一结果表明研究组患者采用瑞芬太尼进行手术,脑组织氧代谢率下降,脑组织缺氧耐受性增强,脑电活动下降,剂量依赖性对血管进行扩张,脑血流量增加,脑血管痉挛减轻,脑血流、代谢情况平衡。有相关研究^[17,18]表明 AHH 能够使脑氧代谢率下降,对照组患者 CERO₂ 变化不够显著,分析原因可能是采用硝酸甘油进行 CH,使得患者 HR 增加,氧耗增多。本次研究结果显示,在不同时间点内,两组患者 VADL 指标在正常范围内,且无显著改变,表明采用硝酸甘油、瑞芬太尼进行手术患者组织氧合状态较好,不会出现脑氧供不足、组织缺氧及无氧酵解等现象,这与相关研究结论一致^[19,20]。在术前、术后 3 d、术后 7 d 两组患者的 MMSE 评分均无统计学差异($P>0.05$),术前、术后 7 d 两组患者的 MMSE 评分均高于术后 3 d 的 MMSE 评分($P<0.05$),这说明两种方法均会对认知功能造成一定的影响,但影响程度没有明显差异,随着术后机体代谢能力的恢复,患者的认知功能也可逐渐恢复正常。

综上所述,瑞芬太尼进行 AHH 后行颅内动脉瘤夹闭术效果较好,说明瑞芬太尼能够对 AHH 脑血管痉挛起到预防和改善治疗等作用,改善组织灌注较低等现象,同时还可以维持血流动力学稳定,使脑氧代谢率降低,比硝酸甘油更有优越性。

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