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丙泊酚镇静对颅脑损伤患者脑氧供需平衡的影响*

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摘要 目的:探讨丙泊酚实施不同程度镇静对颅脑损伤患者脑氧供需平衡的影响。**方法:**选择急性闭合性颅脑损伤需行机械通气患者 46 例,随机分为轻度镇静组(A 组),设定目标脑电双频谱指数(BIS)值 75%;中度镇静组(B 组),设定目标 BIS 值 65%。主要观察达设定目标 BIS 值时丙泊酚靶控输注(TCI)浓度、Ramsay 镇静评分、脑氧供需平衡指标颈内静脉血氧饱和度(SjvO₂)和脑氧摄取率(CERO₂)以及心率(HR)、平均动脉压(MAP)。**结果:**两组设定镇静目标需丙泊酚 TCI 浓度有明显差异($P<0.05$),但 Ramsay 评分比较差异无统计学意义;中度镇静组 SjvO₂ 较基础值增加约 12%($P<0.05$),CERO₂ 较基础值下降约 15%($P<0.05$);而轻度镇静组对 SjvO₂ 和 CERO₂ 基础值没有影响。两组 HR 均较基础值减慢($P<0.05$),但对 MAP 均没有影响。**结论:**颅脑损伤患者维持目标镇静 BIS 值 65%,调控丙泊酚靶浓度 1.5-1.6 μg/mL,更有利于改善脑氧供需平衡。

关键词:颅脑损伤;脑电双频谱指数;丙泊酚;靶控输注

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Effects of Propofol on the Brain Oxygen Balance in Traumatic Brain Injury Patients*

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ABSTRACT Objective: To determine the impact of propofol on the brain oxygen balance in traumatic brain injury patients.

Methods: 46 patients who were diagnosed as acute closed traumatic brain injury and needed mechanical ventilation were divided into two groups: Group A (mild sedation), the target Bispectral Index (BIS) value at about 75; Group B (moderate sedation), the target BIS value at about 65. The propofol target controlled infusion (TCI) concentration, Ramsay score, jugular venous oxygen saturation (SjvO₂), cerebral oxygen uptake rate (CERO₂), heart rate (HR) and mean arterial blood pressure (MAP) were mainly observed. **Results:** Propofol TCI concentrations were significantly different between two groups both at T1 (6 hours after onset of sedation) and T2 (12 hours after onset of sedation) time points ($P<0.05$). In group B, compared with basis value, SjvO₂ were significantly increased by 12% ($P<0.05$), and CERO₂ were significantly reduced by 15% ($P<0.05$). While in group A, compared with basis value, SjvO₂ and CERO₂ had no change. **Conclusion:** Using 1.5-1.6 μg/mL propofol TCI concentration to maintain target sedation BIS value at 65 is more beneficial to balance brain oxygen supply and demand.

Key words: Traumatic brain injury; Bispectral index; Propofol; Target controlled infusion

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前言

颅脑损伤患者脑组织缺血缺氧是继发脑损害最主要因素,临床研究表明^[1,2]80%-90%颅脑损伤死亡患者存在脑缺血、缺氧。因此,维持脑组织氧供需平衡已成为救治脑损伤患者重要措施和关注重点^[3,4]。在 ICU,颅脑损伤患者通常需行机械呼吸维持,并给予不同程度镇静。丙泊酚不仅具有起效快、作用时间短、消除迅速和抗焦虑更满意等特点^[5,6],而且还可降低脑代谢、改善细胞线粒体钠泵功能、防止脑水肿和减轻脑损伤作用^[7,9],因此丙泊酚是颅脑损伤患者较适宜的镇静药。但应用丙泊酚实

施不同程度的镇静对脑氧供需平衡的影响尚不清楚。本研究采用脑电双频谱指数(Bispectral index, BIS)监测,调控丙泊酚不同程度镇静,探讨其对颅脑损伤患者脑氧供需平衡的影响,以期

1 材料与方法

1.1 一般资料

本研究获得医院伦理委员会批准同意并得到患者及家属同意。选择经 CT 检查诊断为急性闭合性颅脑损伤,均行气管插管或气管切开,需行机械通气患者 46 例,其中男 30 例,女

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16例,年龄23-57岁,均于伤后24h之内收住入院,入院时格拉斯哥计分(Glasgow scores, GCS)≤8分。颅脑损伤患者按常规给予脱水利尿、糖皮质激素和抗感染等对症处理。体重指数过高或过低的患者,肝肾功能障碍,心功能不全,循环不稳定需应用血管活性药物,低蛋白血症,长期服用抗抑制药或镇静镇痛药的患者,排除纳入本研究。

1.2 研究方法

患者随机分为两组:A组22例,B组24例。A组(轻度镇静组):男16例,女6例,平均年龄 37.6 ± 13.1 岁,平均体重 63.7 ± 8.3 kg, GCS评分 5.7 ± 1.3 分,使用Diprifusor靶控输注(Target controlled infusion, TCI)系统(英国AstraZeneca公司),初始设定输注丙泊酚靶浓度为 $1.0 \mu\text{g/mL}$,依据BIS值调整丙泊酚,使目标镇静BIS值维持在75%左右;B组(中度镇静组):男14例,女10例,平均年龄 39.1 ± 12.7 岁,平均体重 60.3 ± 9.2 kg, GCS评分 5.3 ± 1.5 分,TCI初试设定输注丙泊酚靶浓度为 $1.5 \mu\text{g/mL}$,继后调整靶浓度使目标镇静BIS值维持在65%。两组患者机械通气模式为同步间歇指令通气(Synchronized intermittent mandatory ventilation, SIMV),设定吸入氧浓度40%,潮气量8-10 ml/kg,呼吸频率12-15次/min,吸/呼为1:2,维持动脉二氧化碳分压(Partial pressure of carbon dioxide in artery, PaCO_2)35 mmHg左右。

1.3 监测指标

常规监测患者的心电图、血压、呼吸、脉搏氧饱和度(Pulse oxygen saturation, SpO_2)和鼻咽温(Nasopharyngeal temperature, T)等生理指标。按Ramsay镇静评分标准分级^[10]:I级,患者焦虑

烦躁不安;II级,安静合作,定向准确;III级,嗜睡,仅对指令有反应;IV级,入睡,轻叩眉间反应敏捷;V级,入睡,轻叩眉间反应迟钝;VI级,深睡,对刺激无反应。按文献^[11,12]从非颅脑损伤侧行颈内静脉逆行穿刺置管,置导管顶端至颈内静脉球部,即体表乳头水平,备用采集颈静脉球血样做血气检测。

1.4 指标评估和记录

双盲法评估和记录应用丙泊酚镇静前(T0)和镇静后6h(T1)、12h(T2)时的心率(Heart rate, HR)、平均动脉压(Mean arterial blood pressure, MAP)、 SpO_2 、鼻咽温和丙泊酚靶浓度、BIS值、Ramsay评分;采集颈静脉球和外周动脉血样行血气分析,获颈内静脉血氧饱和度(Jugular venous oxygen saturation, SjvO_2),按公式计算脑氧摄取率(Cerebral oxygen uptake rate, CERO_2)^[11], $\text{CERO}_2 = \text{AVDO}_2 \div \text{CaO}_2 = 1 - \text{CjvO}_2 \div \text{CaO}_2 = 1 - \text{SjvO}_2 \div \text{SaO}_2$ 。

1.5 统计学分析

采用SPSS 13.0软件进行统计学分析,计量资料以均数±标准差($\bar{x} \pm s$)表示,组间和组内比较采用单因素方差分析,方差不齐则采用秩和检验, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者基本情况

两组患者年龄、性别、体重和GCS评分分布差异无统计学意义;两组间的T、HR、MAP差异也无明显统计差异,但两组T1和T2时间点的HR均较T0明显减慢($P < 0.05$),见表1。

表1 两组患者心率、平均动脉压和体温变化情况比较($\bar{x} \pm s$)

Table 1 Comparison of the changes of HR, MAP and nasopharyngeal temperature of two groups of patients ($\bar{x} \pm s$)

Groups	Time	HR (/min)	MAP (mmHg)	T (°C)
A	T0	87.3 ± 11.2	106.0 ± 12.3	36.8 ± 0.31
	T1	$75.7 \pm 9.4^*$	102.7 ± 10.8	36.7 ± 0.32
	T2	$73.5 \pm 8.7^*$	103.4 ± 10.1	36.7 ± 0.29
B	T0	88.5 ± 12.3	105.3 ± 11.7	36.9 ± 0.29
	T1	$74.6 \pm 8.7^*$	101.2 ± 9.8	36.8 ± 0.29
	T2	$72.5 \pm 9.1^*$	102.0 ± 10.3	36.8 ± 0.30

Note: Compared with T0 time point of the corresponding group, $*P < 0.05$.

2.2 两组丙泊酚 TCI、Ramsay 评分和 BIS 值

两组间T1和T2两个时间点丙泊酚TCI浓度比较有明显差异($P < 0.05$);Ramsay评分组内比较差异有统计学意义($P < 0.05$),但两组间比较无明显统计学差异;BIS值组内T1和T2与T0比较,以及A、B两组患者T1和T2两时间点比较差异均有统计学意义($P < 0.05$),见表2。

2.3 两组动脉血气和 SjvO_2 、 CERO_2 变化

两组间和组内自身动脉血气pH、动脉氧分压(Partial pressure of oxygen in artery, PaO_2)、 PaCO_2 和碱剩余(base excess, BE)比较差异均没有统计学意义。两组基础值(T0) SjvO_2 和 CERO_2 相仿,A组T1和T2与T0比较, SjvO_2 变化无统计学意义;而B组T1和T2与T0比较, SjvO_2 增高明显($P < 0.05$)。 CERO_2 在A组各时间点变化无统计学意义;在B组T1和T2较T0明显

降低($P < 0.05$),与A组对应时间点T1和T2比较,B组 CERO_2 降低更明显,差异有统计学意义($P < 0.05$),见表3。

3 讨论

ICU患者,尤其是接受机械通气患者,镇静治疗将有助于患者舒适安逸、减轻焦虑,耐受气管插管和减轻不适,而合适的镇静深度和客观的评价指标是实现理想镇静治疗的前提和基础。在ICU临床评估镇静指标中,Ramsay评分应用广泛,通常以Ramsay评分3-4分、患者安静、容易唤醒、维持正常睡眠和觉醒周期作为理想镇静目标。但Ramsay评分无法连续应用,对镇静状态缺乏具体和特异性描述,并且是通过刺激觉醒反应而不是评估无刺激状态下的意识水平来实现,即易受评估者和被评估者双方主观因素影响^[13]。因此,需选择更为客观科学的评

表 2 两组患者各时间点 BIS 值、丙泊酚 TCI 浓度和 Ramsay 评分比较($\bar{x} \pm s$)Table 2 Comparison of the BIS values, propofol TCI concentrations and Ramsay scores between two groups of patients at each time point ($\bar{x} \pm s$).

Time	Group	BIS values	Propofol TCI (ug/mL)	Ramsay (scores)
T0	A	93.1± 3.2	0	2.5± 0.35
	B	94.0± 3.5	0	2.6± 0.40
T1	A	75.3± 3.9*	1.1± 0.21	3.4± 0.27*
	B	67.2± 3.8**	1.6± 0.20 [#]	4.0± 0.31*
	A	74.6± 3.5*	1.0± 0.23	3.5± 0.29*
	B	66.3± 3.8**	1.5± 0.22 [#]	4.2± 0.33*

Note: Compared with T0 time point of the corresponding group, * $P<0.05$; Compared with the corresponding time point of group A, [#] $P<0.05$.表 3 两组患者动脉血气和 SjvO₂、CERO₂ 变化情况比较($\bar{x} \pm s$)Table 3 Comparison of the arterial blood gas, SjvO₂ and CERO₂ between two groups of patients at each time point ($\bar{x} \pm s$)

Time	Group	pH	PaO ₂ (mmHg)	PaCO ₂ (mmHg)	BE (mmol/L)	SjvO ₂ (%)	CERO ₂ (%)
T0	A	7.38± 0.03	97.8± 9.3	34.2± 2.3	0.31± 1.7	59.5± 6.2	40.1± 5.9
	B	7.39± 0.03	95.3± 8.7	35.1± 2.6	0.53± 1.5	58.1± 6.3	41.2± 6.1
T1	A	7.37± 0.02	98.1± 8.7	34.7± 2.4	0.42± 1.3	60.3± 6.1	39.7± 6.0
	B	7.38± 0.03	97.0± 7.6	35.0± 2.7	0.47± 1.5	64.8± 7.2*	35.2± 6.2**
T2	A	7.38± 0.03	98.7± 7.8	34.9± 2.1	0.41± 1.3	60.1± 6.3	39.4± 6.1
	B	7.38± 0.03	97.3± 8.1	34.8± 2.5	0.46± 1.4	65.0± 7.5*	35.7± 6.3**

Note: Compared with T0 time point of the corresponding group, * $P<0.05$; Compared with the corresponding time point of group A, [#] $P<0.05$.

价指标。BIS 监测是评估患者遗忘和意识状态的较好方法,是调整镇静药物用量的有效依据,使药量更合理,苏醒更迅速^[14,15]。BIS 监测是被镇静指南唯一列入的客观评估指标,在 ICU 应用中受到广泛关注和认可^[16,17]。然而,也有学者认为 BIS 存在较高的个体间和个体自身变异度,故不能替代基于标准评分系统的临床镇静评估^[18]。此外,不同的镇静药(氯胺酮、右美托咪定等)会影响 BIS 值的敏感性和特异性^[19]。

本研究应用 Ramsay 评分和 BIS 监测这两种指标作比较,指导丙泊酚 TCI 实施不同程度镇静。TCI 是近年来出现一种新的给药方式,是参考病人的体重、年龄,利用药物代谢模型制定的个体给药方案,具有精度高、可控性好特点,能较平稳控制血药浓度和减轻药物对循环和呼吸系统的影响^[20,21]。观察结果显示采用 BIS 监测,设定目标镇静 BIS 值 75 % 和 65 % 两种不同程度镇静,对应丙泊酚 TCI 浓度分别为 1.0-1.1 $\mu\text{g/mL}$ 和 1.5-1.6 $\mu\text{g/mL}$,具有良好相关性;且两组患者 HR 均明显减慢,而 MAP 无明显变化。结果表明应用丙泊酚 TCI 浓度 1.5-1.6 $\mu\text{g/mL}$,维持 BIS 值 65 % 左右,患者舒适安逸、焦虑减轻、氧耗降低、达理想镇静效果。本研究设定的两组不同程度镇静,丙泊酚 TCI 浓度和 BIS 值均有明显差异,但 Ramsay 评分两组间比较差异不明显,与丙泊酚 TCI 浓度和 BIS 值缺乏良好相关性,进一步说明 Ramsay 评分标准较为粗略,对镇静评估界限比较模糊,缺乏敏感性和特异性^[13]。然而,Kasuya Y 等^[19]比较丙泊酚镇静与警觉评分 (Observer's assessment of alertness/sedation, OAA/S)与 BIS 的相关性,发现两者具有较好的相关性,OAA/S 评分 3、4 时,对应 BIS 值分别为 67(64-70) % 和 78(71-84.5) %,与本研究观察结果相似。但作者同时也指出由于 OAA/S 评分

需外部刺激评估患者精神状态,也存在不足。因此,选择 BIS 监测指导评估合适镇静治疗更具客观性和科学性^[22-24]。

颅脑损伤患者救治中,通常需给予一定程度的镇静维持机械呼吸,既能减轻不适焦虑,又能降低脑氧耗。丙泊酚作为短效镇静药,具有起效快、作用时间短、苏醒快等优点,可避免药物对颅脑损伤患者病情评估,因此被推荐用于颅脑损伤患者的镇静^[25,26]。应用丙泊酚实施镇静可降低脑代谢,防止脑水肿^[27,28]。但实施不同程度的镇静,对脑氧供需平衡的影响尚不清楚。颅脑损伤后组织缺血缺氧和奢侈灌注均是继发性脑损害的主要因素,因此维持脑组织氧供需平衡是救治颅脑损伤患者重要措施和关注重点^[3]。本研究参考 Getting 方法行颈内静脉穿刺逆行置管,间断采集颈静脉球部的血样,检测 SjvO₂,计算 CERO₂,较监测颅内压(Intracranial pressure, ICP)、脑灌注压(Cerebral perfusion pressure, CPP)和脑血流量(Cerebral blood flow, CBF),更能客观反映脑组织的氧供需平衡关系,及早发现脑缺血缺氧^[29,30]。观察结果显示应用 TCI 系统泵注丙泊酚 1.5-1.6 $\mu\text{g/mL}$,维持目标镇静 BIS 值 65 %,可使患者的 SjvO₂ 较基础值增高 11.9 % ($P<0.05$),CERO₂ 降低 14.6 % ($P<0.05$),表明应用丙泊酚实施较深镇静,具有降低脑组织氧耗,改善脑组织氧合,维持脑血流与脑氧耗匹配关系,防止脑组织缺血缺氧,产生脑保护作用^[4]。应用丙泊酚 TCI 浓度 1.0-1.1 $\mu\text{g/mL}$,维持目标镇静 BIS 值 75 %,似乎对 SjvO₂ 和 CERO₂ 没有明显影响,提示应用丙泊酚实施较浅镇静,对改善脑组织氧供作用不明显。

我们以往临床观察发现^[29]过度通气(PaCO_2 小于 30 mmHg)可影响脑血流及代谢,致脑氧供需失衡,有潜在脑缺血缺氧危险。Meng L 等^[31]研究认为过度通气(呼气末 CO_2 分压 25

mmHg),可引起脑血管收缩,增加脑血管阻力,降低脑血流及脑组织血氧饱和度,不利于脑组织氧供和氧合。本研究中,两组患者 PaCO_2 维持在 35 mmHg 左右,pH、 PaO_2 和 BE 均基本正常,因此可排除 PaCO_2 、pH 和 PaO_2 对两组患者 SjvO_2 和 CERO_2 的影响。而维持 PaCO_2 35 mmHg 既可保持脑氧供需平衡,又能维持和降低颅内压^[29],这也正是颅脑损伤患者治疗所希望。体温变化也是影响脑氧耗、脑代谢重要因素,本研究两组患者在观察期间体温维持基本正常,且组间和组内也均无差异,故可避免体温变化对脑血流代谢影响。

本研究的局限性之一:临床患者通常镇静和镇痛联合应用,而为了较为准确和严谨的评估丙泊酚镇静对脑氧供需平衡的影响,排除镇痛对脑代谢的干扰,故没有联合应用镇痛药物;局限性之二:颈内静脉穿刺逆行置管检测 SjvO_2 ,系有创监测,但操作并不复杂,且较经颅脑氧饱和度检测方法结果可靠,重复性好。

总之,本研究结果表明颅脑损伤患者机械通气期间,应用 BIS 监测,指导丙泊酚镇静,较依据 Ramsay 评分更敏感客观;维持较深目标镇静 BIS 值 65%,丙泊酚 TCI 浓度 1.5-1.6 $\mu\text{g/mL}$,较浅镇静状态更有利于维持颅脑损伤患者脑氧供需平衡,改善脑氧供,且不影响体循环,具有较好临床应用价值。

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