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右美托咪啶联合咪达唑仑在颅脑创伤中的镇静效果 及对神经内分泌的影响

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摘要 目的:探讨右美托咪啶联合咪达唑仑在颅脑创伤中的镇静效果及对神经内分泌的影响。**方法:**选择 2015 年 3 月至 2016 年 5 月我院收治的 82 例颅脑外伤患者,随机分为对照组(n=41)和观察组(n=41),对照组患者给予丙泊酚联合右美托咪啶镇静治疗,观察组患者则给予右美托咪啶联合咪达唑仑镇静治疗。比较两组患者 24 h 内镇静效率、镇静 1 d 医疗费用及用药前后呼吸循环功能变化、血清皮质醇、 β -内啡肽水平、外周血白细胞计数以及血糖水平。**结果:**观察组镇静 1 d 医疗费用较对照组降低,有统计学差异($P<0.05$),但两组镇静效率比较无统计学差异($P>0.05$)。用药后观察组患者平均动脉压(MAP)、心率(HR)和呼吸频率(RR)分别高于对照组,差异具有统计学意义($P<0.05$),而血氧饱和度(SpO_2)、中心静脉压(CVP)比较无统计学差异($P>0.05$)。用药后两组患者血清皮质醇、 β -内啡肽均较用药前降低,观察组血清皮质醇、 β -内啡肽均高于对照组,差异具有统计学意义($P<0.05$)。用药后观察组患者外周血白细胞计数、血糖水平较用药前降低,对照组患者血糖水平较用药前降低,观察组患者外周血白细胞计数显著低于对照组,差异具有统计学意义($P<0.05$)。**结论:**右美托咪啶联合咪达唑仑应用于颅脑创伤中的镇静效果显著,可有效控制颅脑创伤后的过度应激反应,降低神经内分泌系统紊乱,减少医疗费用,值得临床推广应用。

关键词:颅脑创伤;右美托咪啶;咪达唑仑;镇静效果;神经内分泌

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Sedative Effect of Dexmedetomidine Combined with Midazolam in Cranio-cerebral Trauma and its Influence on Neuroendocrine Function

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ABSTRACT Objective: To investigate the sedative effect of dexmedetomidine combined with midazolam in craniocerebral trauma and its influence on neuroendocrine function. **Methods:** 82 patients with craniocerebral trauma treated in our hospital from March 2015 to May 2016 were selected. They were randomly divided into control group (n=41) and observation group (n=41). The control group received propofol and dexmedetomidine sedation, the observation group received dexmedetomidine combined with midazolam sedation. The sedation efficiency within twenty-four hours, medical expenses within one day sedation were compared between the two groups. The respiratory and circulatory function changes, serum cortisol, β -endorphin levels, peripheral blood leukocyte count and blood glucose levels before and after treatment were compared between the two groups. **Results:** The medical expenses within one day sedation in the observation group were lower than that in the control group, the difference was statistically significant ($P<0.05$). There was no statistical difference in the sedation efficiency between the two groups ($P>0.05$). After treatment, the average arterial pressure (MAP), heart rate (HR) and respiratory rate (RR) of the observation group were significantly higher than those in the control group, the differences were statistically significant ($P<0.05$). There was no statistical difference in blood oxygen saturation (SpO_2), central venous pressure (CVP) between the two groups ($P>0.05$). After treatment, the serum cortisol, β -endorphin in the two groups were lower than before treatment. The serum cortisol, β -endorphin in observation group were higher than that in control group, the differences were statistically significant ($P<0.05$). After treatment, the peripheral blood leukocyte count and blood glucose in observation group were lower than before treatment. The blood glucose in control group was lower than before treatment. The peripheral blood leukocyte count in observation group was lower than that in control group, the differences were statistically significant ($P<0.05$). **Conclusion:** Dexmedetomidine combined with midazolam is effective in the treatment of craniocerebral trauma. It can effectively control the excessive stress reaction after craniocerebral trauma, and reduce the neuroendocrine system disorder and medical expenses, which is worthy of clinical application.

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前言

颅脑创伤是临床上常见的急危重症,也是导致患者外伤后死亡的常见原因之一。由于该病患者在治疗过程中会出现剧烈的疼痛,引起患者躁动,对临床治疗产生不利影响^[1-3]。目前,临床上对于颅脑创伤患者多采用镇静治疗,使患者处于“休眠”状态,从而降低患者躁动不安,有利于临床治疗的进行^[4,5]。近年来研究发现,颅脑创伤患者由于剧烈的创伤导致患者神经内分泌系统紊乱,进而增加继发性脑缺血、脑肿胀等严重并发症的发生率,对患者的生命健康造成极大的威胁^[6-8],而镇静可以有效地降低不良刺激和交感神经兴奋度,从而降低神经内分泌系统的影响。右美托咪啶属于一种新型的 α 受体激动剂,具有较强的镇静镇痛作用,同时可有效缓解患者焦虑、不安等负面情绪,且不会严重影响呼吸以及脑循环,是目前临床上应用较为广泛的药物之一^[9,10]。然而,单独使用右美托咪啶治疗颅脑创伤患者的效果并不十分理想。咪达唑仑同样具有显著的镇静镇痛效果,与右美托咪啶联合应用可能发挥协同作用,从而提高临床治疗颅脑创伤患者的效果^[11]。本研究探讨右美托咪啶联合咪达唑仑在颅脑创伤中对神经内分泌的影响及其镇静效果,旨在有效治疗颅脑创伤患者提供参考依据,现作如下报道。

1 资料与方法

1.1 一般资料

选择 2015 年 3 月~2016 年 5 月我院收治的颅脑外伤患者 82 例,纳入标准:(1)所有患者受伤时间在 12 h 内;(2)年龄 ≥ 18 岁;(3)格拉斯哥评分(Glasgow coma scale, GCS)^[12]在 6~13 分;(4)单独采用右美托咪啶方案效果不理想;(5)患者或家属知情同意并签署知情同意书。排除标准:(1)对本研究相关药物存在过敏者;(2)合并肝、肾等脏器功能严重障碍者;(3)妊娠期或哺乳期妇女;(4)24 h 内需接受开颅手术治疗者;(5)既往有吸毒史或吸烟酗酒者。所有患者随机分为对照组($n=41$)和观察组($n=41$),其中观察组男 24 例,女 17 例,年龄 23~71 岁,平均年龄(42.3 ± 5.1)岁;交能事故伤 21 例,高处坠落伤 13 例,暴力伤 7 例;开放伤 33 例,闭合伤 8 例;入院后 GCS 评分为(10.23 ± 1.92)分。对照组男 23 例,女 18 例,年龄 24~72 岁,平均年龄(42.5 ± 5.2)岁;交能事故伤 23 例,高处坠落伤 12 例,暴

力伤 6 例;开放伤 32 例,闭合伤 9 例;入院后 GCS 为(10.16 ± 1.88)分。两组患者一般资料对比无显著性差异($P>0.05$),具有可比性。研究经医院伦理委员会批准。

1.2 研究方法

所有患者均予以右美托咪啶镇静:取 200 μg 的右美托咪啶(江苏恒瑞医药股份有限公司,国药准字:H20090248,规格 2 mL:0.2 mg)加入 50 mL 的 0.9% 的氯化钠溶液中,以 0.5 $\mu\text{g}/\text{kg}/\text{h}$ 的速率进行输送。对照组患者在此基础上给予丙泊酚(西安力邦制药有限公司国药准字:H20040300,规格:50 升/瓶)镇静,具体用法如下:起始泵入速率为 2 mg/kg/h,根据患者的镇静评分予以适当的调整,调整范围在 0.3~4.0 mg/kg/h 之间。观察组患者则予以咪达唑仑(宜昌人福药业有限责任公司,国药准字:H20067041,规格:2 mL:10 mg)镇静,具体用法如下:起始泵入速率为 0.1 mg/kg/h,根据患者的镇静评分予以适当的调整,调整范围在 0.02~0.2 mg/kg/h 之间。对所有患者均进行 1 d 的观察。

1.3 观察指标

比较两组 24 h 内镇静效率、镇静 1 d 医疗费用,其中镇静效率 = (维持患者镇静躁动评分 2~4 分的时间 / 总镇静时间) $\times 100\%$ 。观察用药前后平均动脉压(mean arterial pressure, MAP)、心率(heart rate, HR)、呼吸频率(respiratory rate, RR)、血氧饱和度(blood oxygen saturation, SpO_2)、中心静脉压(Central venous pressure, CVP)水平的变化。于用药前、用药后采集患者外周静脉血 2 mL,注入 EDTA 抗凝试管中,在常温下 3500 r/min 离心 10 min,提取上清,应用放射免疫法测定血清皮质醇、 β -内啡肽水平,试剂盒购自北京康源瑞生物技术有限公司,操作参照说明书进行。外周血白细胞计数采用全自动血液分析仪测定,血糖水平应用罗氏全自动血糖分析仪测定。

1.4 统计学方法

采用 SPSS20.0 进行统计分析,血清皮质醇、 β -内啡肽等计量资料以($\bar{x} \pm s$)表示,采用 t 检验,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组镇静效率及镇静 1 d 医疗费用比较

两组镇静效率比较无统计学差异($P>0.05$),观察组镇静 1 d 医疗费用较对照组显著降低,有统计学差异($P<0.05$),见表 1。

表 1 两组镇静效率及 1 d 使用费用对比($\bar{x} \pm s$)

Table 1 Comparison of sedation efficiency and medical expenses within one day sedation between the two groups($\bar{x} \pm s$)

Groups	n	Sedation efficiency(%)	Medical expenses within one day sedation(RMB)
Observation group	41	86.21 $\pm$ 8.14	424.45 $\pm$ 114.63
Control group	41	86.55 $\pm$ 8.33	561.25 $\pm$ 185.23
t	-	0.166	4.019
P	-	0.869	0.000

2.2 两组患者呼吸循环功能变化情况比较

用药前两组患者 MAP、HR、RR、SpO₂、CVP 水平比较无统计学差异(P>0.05),用药后两组患者 MAP、HR 和 RR 较用药

前均降低,观察组患者 MAP、HR 和 RR 高于对照组,有统计学差异(P<0.05),而 SpO₂、CVP 比较无统计学差异(P>0.05),见表2。

表 2 两组患者呼吸循环功能变化情况比较($\bar{x} \pm s$)

Table 2 Comparison of respiratory and circulatory function changes between the two groups($\bar{x} \pm s$)

Groups	Observation group(n=41)		Control group(n=41)	
	Before treatment	After treatment	Before treatment	After treatment
MAP(mmHg)	105.23± 4.22	97.15± 4.34* [#]	105.72± 4.13	90.69± 3.54*
HR(n/min)	103.21± 12.82	82.64± 10.93* [#]	102.75± 12.64	76.52± 10.35*
RR(n/min)	22.80± 2.34	20.21± 2.63* [#]	22.65± 2.44	18.45± 2.84*
SpO ₂ (%)	98.92± 1.62	98.61± 1.97	98.84± 1.72	98.45± 1.83
CVP(mmHg)	9.86± 1.92	9.76± 1.88	9.83± 1.78	9.78± 1.79

Note: Compared with before treatment, *P<0.05; Compared with bcontrol group, [#]P<0.05.

2.3 两组患者神经内分泌指标比较

用药前两组患者血清皮质醇、β-内啡肽比较无统计学差异(P>0.05),用药后两组患者血清皮质醇、β-内啡肽均较用药前

降低,观察组血清皮质醇、β-内啡肽均高于对照组,差异具有统计学意义(P<0.05),见表3。

表 3 两组患者神经内分泌指标比较($\bar{x} \pm s$)

Table 3 Comparison of neuroendocrine indexes between the two groups($\bar{x} \pm s$)

Groups	n	Serum cortisol(ng/mL)		β-endorphin(pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	41	278.48± 132.34	141.2± 52.13*	304.3± 57.20	292.8± 26.44*
Control group	41	280.11± 130.83	102.8± 81.65*	305.2± 56.81	267.1± 24.72*
t	-	0.059	2.538	0.071	2.934
P	-	0.954	0.013	0.943	0.000

Note: Compared with before treatment, *P<0.05.

2.4 两组患者外周血白细胞计数及血糖水平比较

用药前两组患者外周血白细胞计数、血糖水平比较差异无统计学意义(P>0.05),用药后观察组上述指标为(9.15± 5.24)

× 10⁹/L、(6.93± 2.12)mmol/L,对照组为(12.73± 3.87)× 10⁹/L、(6.88± 2.04)mmol/L,两组外周血白细胞计数比较有统计学差异(P<0.05),见表4。

表 4 两组患者外周血白细胞计数及血糖水平比较($\bar{x} \pm s$)

Table 4 Comparison of peripheral blood leukocyte count and blood glucose level between the two groups($\bar{x} \pm s$)

Groups	n	Peripheral blood leukocyte count(× 10 ⁹ /L)		Blood glucose(mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	41	13.84± 4.25	9.15± 5.24*	8.14± 2.52	6.93± 2.12*
Control group	41	13.91± 4.33	12.73± 3.87	8.13± 2.45	6.88± 2.04*
t	-	0.107	2.879	0.007	0.221
P	-	0.915	0.001	0.974	0.826

Note: Compared with before treatment, *P<0.05.

3 讨论

对于颅脑创伤患者,尽快明确伤后的神经内分泌情况并予以针对性干预措施,有效防止颅脑创伤后继发损伤是非常必要的^[13,14]。近年来随着镇静镇痛理念的逐渐推广应用,镇静镇痛干预已成为临床上用以控制颅脑创伤引发病理生理损伤发生的

主要方式,可有效缓解剧烈应激因素引发的进一步损伤,有利于临床治疗及患者的康复^[15]。目前重症脑损伤治疗专家提出:镇静镇痛是颅脑创伤患者治疗过程中必不可少的部分,其主要目标是为患者提供足够的脑保护,同时提高患者舒适度,缓解应激反应,为临床的医护操作提供有利条件^[16-18]。由此,寻找一种最佳的镇静镇痛方案已成为目前临床上关注的重点。右美托

咪唑可作用于脑干蓝斑核 $\alpha 2$ 受体上,有效抑制了去甲肾上腺素的产生和释放,从而起到镇静、催眠及抗焦虑的功效^[19]。咪唑啉仑作为一种强效的镇痛药物,其镇静、抗焦虑作用较为明显,且在临床上广泛应用,两者用于颅脑创伤患者的镇静镇痛治疗中各有优势^[20,21]。因此,本文通过探讨右美托咪唑联合咪达唑仑在颅脑创伤中的镇静效果及对神经内分泌的影响,旨在为两者联合应用于颅脑创伤患者治疗提供理论依据。

本研究结果显示:两组镇静效率比较无统计学差异($P>0.05$),观察组镇静1d内医疗费用显著低于对照组($P<0.05$)。这与许涛等人的研究报道相一致^[22],表明了右美托咪唑联合咪达唑仑应用于颅脑创伤中的镇静效果相当,且能有效减轻患者的经济负担,具有一定的经济效益。另外,用药后观察组患者MAP、HR和RR高于对照组($P<0.05$),而 SpO_2 、CVP比较无统计学差异($P>0.05$)。这表明了右美托咪唑联合咪达唑仑应用于颅脑创伤中具有较高的安全性,不会对患者的循环呼吸系统产生明显的抑制作用,从而有效降低了血压下降以及呼吸暂停等不良反应发生的风险。分析原因,我们认为这主要与咪达唑仑起效快、作用时间较短,患者苏醒更为迅速有关^[23,24]。此外,有研究报道认为 β -内啡肽水平在应激反应的调控过程中起着至关重要的作用,与镇痛、神经情绪活动以及神经损伤和修复均存在密切关联。而 β -内啡肽的表达过度可能会对患者大脑皮质、呼吸以及心血管运动等神经中枢产生更强的抑制作用,而对其是否应实施早期有效控制尚且存在一定的争议^[25,26]。但另有研究学者认为早期在一定程度上增高血浆 β -内啡肽水平对患者是有益的。本研究提示用药后观察组患者血清皮质醇、 β -内啡肽较对照组升高,具有显著性差异($P<0.05$),表明了右美托咪唑联合咪达唑仑应用于颅脑创伤中可有效控制患者应激反应,分析原因,我们认为 β -内啡肽具有较强的镇痛作用,可通过诱导患者产生兴奋、愉悦等情绪,从而在一定程度上减轻疼痛所导致的不良应激反应。与此同时, β -内啡肽可对促肾上腺皮质激素以及糖皮质激素的分泌产生抑制作用,进一步防止下丘脑-垂体-肾上腺轴和交感神经的兴奋过度,最终达到缓解应激反应的作用^[27,28]。本文结果还显示了在用药后观察组患者外周血白细胞计数低于对照组,具有显著性差异($P<0.05$),这充分证明了上述结果,表明了右美托咪唑联合咪达唑仑应用于颅脑创伤中可有效控制患者的应激反应^[29,30]。

综上所述,右美托咪唑联合咪达唑仑应用于颅脑创伤中的镇静效果较佳,具有较好的经济效益,且能有效控制患者的应激反应,改善呼吸循环功能,安全性较好,可为临床颅脑创伤镇静治疗提供参考。

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