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右美托咪定在颅脑外伤手术患者中的脑保护作用及其对应激反应和炎症因子的影响*

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摘要 目的：探讨右美托咪定在颅脑外伤手术患者中的脑保护作用及其对应激反应和炎症因子的影响。**方法：**选取四川绵阳四〇四医院于 2016 年 1 月 -2017 年 12 月期间收治的重型颅脑外伤患者 136 例为研究对象。根据随机数字表法将患者分为对照组（n=68）与研究组（n=68），其中对照组手术时给予咪唑安定静脉滴注，研究组手术时给予右美托咪定静脉滴注，比较两组患者术前（T1）、术后 24 h（T7）血浆 S-100β 蛋白、神经元特异性烯醇化酶（NSE）、脑氧摄取率（$CERO_2$）、动脉 - 颈内静脉血氧含量差（$Da\text{-}jvO_2$）、颈静脉血氧饱和度（$SjvO_2$）水平，桡动脉成功穿刺时（T2）、气管插管时（T3）、上开口器时（T4）、手术结束时（T5）、拔管时（T6）皮质醇（COR）、肾上腺素（E）、血糖（GLU）水平，T2、T5、T7 白细胞介素 -6（IL-6）、白细胞介素 -10（IL-10）、肿瘤坏死因子 -α（TNF-α）水平。**结果：**两组患者 T7 时 S-100β 蛋白、NSE 较 T1 时显著升高，但研究组低于对照组（P<0.05）。两组患者 T7 时 $CERO_2$、$Da\text{-}jvO_2$ 较 T1 时降低，且研究组低于对照组，$SjvO_2$ 较 T1 时升高，且研究组高于对照组（P<0.05）。在 T4-T6 时间点时，研究组 GLU 显著低于对照组，在 T3-T6 时间点时，研究组 COR、E 显著低于对照组（P<0.05）。两组患者 T5、T7 时 IL-6、IL-10、TNF-α 均较 T2 时升高，且研究组 T5、T7 时 IL-6、TNF-α 低于对照组，IL-10 高于对照组（P<0.05）。**结论：**相对咪唑安定而言，在颅脑外伤手术中使用右美托咪定可显著减少脑损伤，降低炎症因子水平，且患者应激反应较小。

关键词：右美托咪定；咪唑安定；颅脑外伤；脑保护；应激反应；炎症因子
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Effect of Dexmedetomidine on Brain Protection and Its Effect on Stress Response and Inflammatory Factors of Patients in the Operation of Craniocerebral Trauma*

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ABSTRACT Objective: To investigate the effect of dexmedetomidine on brain protection and its effect on stress response and inflammatory factors of patients in the operation of craniocerebral trauma. **Methods:** 136 patients with severe craniocerebral trauma who were treated in our hospital from January 2016 to December 2017 were selected as the research subjects, and the patients were divided into the control group (n=68) and the study group (n=68) according to the random digital table. The control group was given midazolam by intravenous drip during the operation, the study group was given dexmedetomidine by intravenous drip during the operation. The plasma S-100β protein, neuron specific enolase (NSE), cerebral extraction of oxygen ($CERO_2$), arterio-jugular difference of oxygen ($Da\text{-}jvO_2$) and jugular venous oxygen saturation ($SjvO_2$) levels of two groups before operation (T1), postoperative 24 h (T7) were compared, cortisol (COR), adrenaline (E) and blood glucose (GLU) levels at successful puncture of radial artery(T2), endotracheal intubation (T3), upper opening device (T4), end of operation (T5), extubation (T6) were compared, and the levels of interleukin-6 (IL-6), interleukin-10 (IL-10) and tumor necrosis factor-α (TNF-α) at T2, T5, T7 were compared. **Results:** S-100β protein and NSE of patients in the two groups at T7 were significantly higher than those of T1, but the study group was lower than the control group (P<0.05). $CERO_2$ and $Da\text{-}jvO_2$ of patients in the two groups at T7 was lower than that of T1, and the study group was lower than the control group, $SjvO_2$ was higher than that of T1, and the study group was higher than that of the control group (P<0.05). At the time point of T4-T6, GLU of the study group was significantly lower than the control group, at the time point of T3-T6, the COR and E of the study group were significantly lower than the

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control group (P<0.05). The levels of IL-6, IL-10 and TNF-α in the two groups at T5 and T7 were higher than those of T2, the IL-6 and TNF-α in the study group at T5 and T7 were lower than those in the control group, and the IL-10 was higher than that of the control group (P<0.05). **Conclusion:** Compared with midazolam, dexmedetomidine can significantly reduce brain injury and reduce inflammatory factors in patients with craniocerebral trauma, and the stress response is relatively small.

Key words: Dexmedetomidine; Midazolam; Craniocerebral trauma; Brain protection; Stress response; Inflammatory factors

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前言

近年来随着建筑、交通运输业等经济活动的不断发展,因外力直接或间接作用于头部引起的颅脑损伤发病率逐年升高[1,2]。该患者临床表现为头痛、恶心、意识障碍、肢体瘫痪等,严重时甚至将发生脑氙而危及患者生命,给患者带来极大的安全隐患[3-5]。颅脑损伤患者根据格拉斯哥昏迷评分(Glasgow coma score,GCS)分为 3 种类型:轻型、中型、重型,其中重型颅脑损伤救治最为困难,病死率极高,临床上主要治疗原则为紧急抢救、纠正休克、抗感染以及手术治疗,然而颅脑部位实施手术时,易对患者脑部进行二次损伤,且术中会产生较强的应激反应,因此,术中选择合适的麻醉药物可减轻继发性损伤,进而改善患者预后[6-8]。右美托咪定与咪唑安定是临床常用的麻醉辅助用药[9,10],目前关于二者在颅脑损伤患者中围术期持续应用的效果尚不十分明确。鉴于此,本研究通过探讨右美托咪定在颅脑外伤手术中对患者的脑保护作用及其对应激反应和炎症因子的影响,旨在为临床选择合适的麻醉药物提供数据参考,现作如下报道。

1 资料与方法

1.1 一般资料

选取四川绵阳四〇四医院于 2016 年 1 月 -2017 年 12 月期间收治的重型颅脑外伤患者 136 例为研究对象。纳入标准:(1)所有患者均经 CT 检查确诊;(2)未长期服用镇静镇痛药物者;(3) 身体其余部位无严重创伤者;(4) 美国麻醉医师协会(American Society of Anesthesiologists,ASA) 分级为Ⅰ-Ⅱ级者;(5)所有患者均知情本研究并签署同意书。排除标准:(1)伴有心、肺、肾等脏器病变者;(2)伴有上呼吸道感染者;(3)伴有精神病病史者。根据随机数字表法将患者分为对照组(n=68)与研究组(n=68),其中对照组男 38 例,女 30 例;年龄 20-61 岁,平均(35.78± 3.79)岁;病程 3-16 h,平均(8.19± 1.46)h;受伤原因:车祸伤 41 例,坠落伤 15 例,打击伤 12 例。研究组男 35 例,女 33 例;年龄 21-63 岁,平均(34.28± 4.02)岁;病程 2-17 h,平均(8.56± 1.52)h;受伤原因:车祸伤 39 例,坠落伤 16 例,打击伤 13 例。两组患者一般资料比较无统计学差异(P>0.05),均衡可比。本研究经四川绵阳四〇四医院伦理委员会批准同意。

1.2 方法

患者入室后监测心电图、脉搏、血氧饱和度,建立静脉通路、吸氧,其中对照组麻醉诱导前给予咪唑安定(江苏恩华药业股份有限公司, 国药准字 H20031071, 规格:5 mL:5 mg)0.1 mg/kg 静脉滴注,之后以 30 μg/(kg·h)滴注至手术结束。研究组则在麻醉诱导前给予右美托咪定(江苏恩华药业股份有限公司,国药准字 H20133331,规格:1 mL: 0.1 mg)1.0 μg/ kg 静脉滴注,之后以 0.5 μg/(kg·h)滴注至手术结束。麻醉诱导采用 1.0-1.5 mg/kg 丙泊酚、0.5 μg/ kg 舒芬太尼、1 mg/kg 苯磺顺阿曲库铵,随之进行气管插管,调整呼吸参数,呼吸末二氧化碳控制范围处于 30-35 mmHg。麻醉维持采用 4-6 mg/(kg·h)异丙酚、0.2-0.4 μg/(kg·h)瑞芬太尼、0.5 mμg/(kg·h)阿曲库胺,同时 BIS 数值维持范围处于 40-60。

1.3 观察指标

分别于术前(T1)、桡动脉成功穿刺时(T2)、气管插管时(T3)、上开口器时(T4)、手术结束时(T5)、拔管时(T6)、术后 24 h(T7)采集患者外周静脉血 10 mL,3000 r/min 离心 6 min,取上清液保存于 -20℃冰箱中待测。于 T1、T7 时采用酶联免疫吸附试验检测血清 S-100β 蛋白、神经元特异性烯醇化酶(neuron-specific enolase,NSE), 试剂盒来源于美国贝克曼库尔特公司。同时记录患者脑氧摄取率 (cerebral extraction of oxygen, $CERO_2$)、动脉 - 颈内静脉血氧含量差(arterio-jugular difference of oxygen,Da-jvO_2)、颈静脉血氧饱和度(jugular venous oxygen saturation,$SjvO_2$)。分别于 T2-T6 时采用酶联免疫吸附试验(试剂盒购自上海雅培生物科技工程有限公司) 检测皮质醇(cortisol,COR)、肾上腺素(epinephrine,E)水平。采用快速血糖仪检测血糖(blood glucose,GLU)水平。分别于 T2、T5、T7 时采用酶联免疫吸附试验 (试剂盒购自上海雅培生物科技工程有限公司)检测白细胞介素 -6(interleukin -6,IL-6)、白细胞介素 -10(interleukin -10,IL-10)、肿瘤坏死因子 -α (tumor necrosis factor-α,TNF-α)水平,以上指标水平的检测均严格按照试剂盒说明书操作。

1.4 统计学方法

采用 SPSS20.0 软件进行数据处理,S-100β 蛋白、NSE 水平、应激反应指标水平以及炎症因子水平等计量资料用($\bar{x}\pm s$)表示,采用 t 检验,性别比例等计数资料用[n(%)]表示,采用 x^2 检验,检验标准设置为α=0.05。

2 结果

2.1 两组患者神经细胞因子比较

两组患者 T1 时 S-100β 蛋白、NSE 比较无统计学差异(P>0.05); 两组患者 T7 时 S-100β 蛋白、NSE 较 T1 时显著升高,但研究组低于对照组(P<0.05);详见表 1。

2.2 两组患者脑氧代谢指标比较

两组患者 T1 时 $CERO_2$、Da-jvO_2、$SjvO_2$ 比较无统计学差异(P>0.05);两组患者 T7 时 $CERO_2$、Da-jvO_2 较 T1 时降低,且研究组低于对照组,$SjvO_2$ 较 T1 时升高, 且研究组高于对照组(P<0.05);详见表 2。

表 1 两组患者 S-100β 蛋白、NSE 比较($\bar{x}\pm s$,μg/L)

Table 1 Comparison of S-100β protein and NSE of patients in two group($\bar{x}\pm s$,μg/L)

Groups	n	S-100β protein		NSE	
		T1	T7	T1	T7
Control group	68	0.07± 0.02	0.36± 0.04*	8.36± 0.52	29.12± 4.17*
Study group	68	0.06± 0.05	0.23± 0.03*	8.37± 0.63	24.41± 4.01*
t		1.531	21.440	0.101	6.714
P		0.128	0.000	0.920	0.000

Note: compared with T1, *P<0.05.

表 2 两组患者 $CERO_2$、$Da\text{-}jvO_2$、$SjvO_2$ 比较($\bar{x}\pm s$)

Table 2 Comparison of $CERO_2$, $Da\text{-}jvO_2$, $SjvO_2$ of patients in two group($\bar{x}\pm s$)

Groups	n	$CERO_2$(%)		$Da\text{-}jvO_2$(mmol/L)		$SjvO_2$(%)	
		T1	T7	T1	T7	T1	T7
Control group	68	33.93± 5.17	30.30± 6.85*	49.23± 5.17	36.84± 6.03*	60.62± 8.22	67.73± 7.84*
Study group	68	34.58± 4.36	24.69± 7.48*	48.87± 6.24	27.19± 6.18*	61.39± 9.31	77.41± 8.36*
t		0.793	4.561	0.366	9.216	0.511	6.965
P		0.429	0.000	0.715	0.000	0.610	0.000

Note: compared with T1, *P<0.05.

2.3 两组患者应激反应比较

两组患者 T2 时间点 GLU、COR、E 比较无统计学差异(P>0.05);在 T4-T6 时间点时,研究组 GLU 显著低于对照组,在 T3-T6 时间点时,研究组 COR、E 显著低于对照组(P<0.05);详见表 3。

表 3 两组患者应激反应比较($\bar{x}\pm s$)

Table 3 Comparison of stress response of patients in two groups ($\bar{x}\pm s$)

Groups	Indexes	T2	T3	T4	T5	T6
Control group (n=68)	GLU(mmol/L)	4.68± 0.45	4.83± 0.42	5.75± 0.35	5.19± 0.48	5.64± 0.51
	COR(μg/L)	227.93± 8.32	248.18± 9.17	240.06± 9.27	236.82± 8.22	252.54± 9.23
	E(mmol/L)	121.58± 10.25	142.20± 9.22	135.75± 8.35	128.89± 9.18	143.14± 7.21
Study group(n=68)	GLU(mmol/L)	4.73± 0.32	4.78± 0.57	4.96± 0.47$^{\&}$	4.52± 0.52$^{\&}$	4.84± 0.43$^{\&}$
	COR(μg/L)	228.58± 8.36	236.87± 9.24$^{\&}$	229.29± 10.31$^{\&}$	221.93± 9.27$^{\&}$	237.73± 8.17$^{\&}$
	E(mmol/L)	118.69± 8.48	127.19± 7.18$^{\&}$	122.31± 9.36$^{\&}$	114.60± 8.35$^{\&}$	131.74± 10.13$^{\&}$

Note: compared with the control group, $^{\&}$P<0.05.

2.4 两组患者炎症因子比较

两组患者 T2 时 IL-6、IL-10、TNF-α 比较无统计学差异(P>0.05);两组患者 T5、T7 时 IL-6、IL-10、TNF-α 均较 T2 时升高,且研究组 T5、T7 时 IL-6、TNF-α 低于对照组,IL-10 高于对照组(P<0.05);详见表 4。

表 4 两组患者炎症因子比较($\bar{x}\pm s$,pg/mL)

Table 4 Comparison of inflammatory factors of patients in two groups($\bar{x}\pm s$, pg/mL)

Groups	Indexes	T2	T5	T7
Control group(n=68)	IL-6	70.69± 15.46	301.47± 38.24$^{\#}$	334.58± 49.36$^{\#}$
	IL-10	41.04± 13.57	60.79± 26.05$^{\#}$	92.69± 19.48$^{\#}$
	TNF-α	31.87± 16.24	96.39± 18.31$^{\#}$	114.93± 15.17$^{\#}$
Study group(n=68)	IL-6	69.19± 14.18	279.41± 28.36$^{\#\&}$	304.30± 44.85$^{\#\&}$
	IL-10	40.28± 17.57	69.64± 20.19$^{\#\&}$	107.85± 216.26$^{\#\&}$
	TNF-α	32.72± 18.48	85.67± 18.28$^{\#\&}$	99.12± 17.22$^{\#\&}$

Note: compared with the control group, $^{\&}$P<0.05; compared with T2, $^{\#}$P<0.05.

3 讨论

临床上重型颅脑损伤患者多存在不同程度的疼痛、焦虑以及躁动等症状，上述症状易引起机体的过度兴奋从而增加脑代谢水平，对患者神经功能造成进一步的损伤，因此，对重型颅脑损伤患者进行必要的镇静治疗极其关键[11-13]。咪唑安定是一种γ氨基丁酸受体激动剂，具有催眠、镇静、抗焦虑等作用，常被用于治疗失眠症或外科手术时诱导睡眠。右美托咪定是一种新型高效的α2 肾上腺素受体激动剂，具有镇痛、催眠、镇静抗交感等作用，与常规麻醉药物相比，右美托咪定用药起效快，且对患者呼吸无抑制作用，可使患者保持随时被唤醒的状态[14-16]。S-100β 蛋白、NSE 主要位于中枢神经系统的胶质细胞中，正常机体血液中含量极少，然而当患者中枢神经受损后，S-100β 蛋白、NSE 被大量释放至人体血液中，临床多通过检测血液中的 S-100β 蛋白、NSE 来判定机体脑部损伤严重程度[17-19]。$CERO_2$ 临床多用于反映大脑耗氧量，当其减少时，表明脑氧代谢率下降[20]；$SjvO_2$ 临床多用于反映脑氧代谢状况，当其水平出现异常升高时则提示脑供氧或者脑血流量增加[21]。

本研究结果发现，两组患者 T7 时 S-100β 蛋白、NSE 较 T1 时显著升高，但研究组低于对照组（P<0.05），表明术后重型颅脑损伤患者仍存在一定的脑损伤，但使用右美托咪定麻醉的患者 S-100β 蛋白、NSE 增加程度相对较低，提示右美托咪定对患者具有一定的脑保护作用。同时两组患者 T7 时 $CERO_2$、$Da\text{-}jvO_2$ 较 T1 时降低，且研究组低于对照组，$SjvO_2$ 较 T1 时升高，且研究组高于对照组（P<0.05），提示在颅脑外伤手术期间，右美托咪定可显著降低患者的脑氧代谢，降低脑供氧量，提高脑组织缺氧耐受性，对患者颅脑形成一定的保护作用。本研究结果还显示，在 T4-T6 时间点时，研究组 GLU 显著低于对照组，在 T3-T6 时间点时，研究组 COR、E 显著低于对照组（P<0.05），说明右美托咪定可缓解患者应激反应。COR、E 对人体的糖、蛋白质以及脂肪代谢起调节作用，可作为患者应激反应的重要敏感指标，另 GLU 也属于临床常用的应激反应指标之一[22-24]。上述应激反应指标发生变化，可能与右美托咪定可通过机体外周的中枢以及α2 产生镇静、镇痛效用有关，同时还可阻碍去甲肾上腺素的释放，从而降低交感神经活性等[25-27]。另外，两组患者 T5、T7 时 IL-6、IL-10、TNF-α 均较 T2 时升高，且研究组 T5、T7 时 IL-6、TNF-α 低于对照组，IL-10 高于对照组（P<0.05），提示右美托咪定可帮助维持炎症细胞因子的相对稳定，继而减轻炎症反应。其主要抗炎机制表现为以下几点[28-30]：（1）通过抑制 NF-kB 活性从而降低炎性因子表达水平；（2）抑制交感神经活动；（3）抑制单核巨噬细胞炎症因子的表达。

综上所述，重型颅脑损伤患者手术期间使用右美托咪定维持麻醉，对脑组织具有一定的保护作用，同时可缓解患者应激反应，减轻炎性反应。

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