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右美托咪啶对急性主动脉夹层患者谵妄及血清 CRP、MMPs、NT-proBNP、NE 水平的影响 *

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摘要 目的：探讨右美托咪啶对急性主动脉夹层患者谵妄及血清 C 反应蛋白（CRP）、基质金属蛋白酶（MMPs）、N 端前脑钠肽（NT-proBNP）、中性粒细胞弹性蛋白酶（NE）水平的影响。**方法：**选择 2014 年 1 月 ~2017 年 1 月我院收治的急性主动脉夹层患者 84 例，根据随机数字表法将其分为对照组（n=42）与研究组（n=42）。对照组入院后给予吗啡镇痛，研究组则给予右美托咪啶镇痛。观察对比两组治疗前与治疗 24 h 后 C 反应蛋白（CRP）、基质金属蛋白酶 -9（MMP-9）、基质金属蛋白酶 -2（MMP-2）、NT-proBNP 和 NE 水平、谵妄的发生率以及脱机持续时间与 ICU 入住时间。**结果：**治疗前两组患者 CRP、MMP-9、MMP-2、NT-proBNP、NE 水平比较无统计学差异（P>0.05），治疗 24h 后研究组 CRP、MMP-9、MMP-2、NT-proBNP、NE 水平低于对照组与治疗前，差异有统计学意义（P<0.05）。研究组术后谵妄的发生率为 7.14%（3/42），低于对照组的 26.19%（11/42），差异有统计学意义（P<0.05）。研究组脱机持续时间与 ICU 入住时间均低于对照组，差异有统计学意义（P<0.05）。**结论：**右美托咪啶不仅具有镇痛、镇静等效应，还对急性主动脉夹层患者炎性反应具有显著的抑制作用，且降低了谵妄的发生率，保证了患者的预后质量。

关键词：右美托咪啶；急性主动脉夹层；谵妄；C 反应蛋白；基质金属蛋白酶；N 端前脑钠肽；中性粒细胞弹性蛋白酶

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Effects of Dexmedetomidine on Delirium and Serum Levels of CRP, MMPs, NT-proBNP and NE in Patients with Acute Aortic Dissection*

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ABSTRACT Objective: To investigate the effects of dexmedetomidine on delirium and serum levels of C reactive protein (CRP), Matrix metalloproteinases (MMPs), N end forebrain natriuretic peptide (NT-proBNP) and neutrophil elastase (NE) in patients with acute aortic dissection. **Methods:** 84 patients with acute aortic dissection who were treated in our hospital from January 2014 to January 2017 were selected, they were divided into the control group (n=42) and the study group (n=42). The control group was given morphine analgesia immediately after admission, while the study group was given dexmedetomidine analgesia. The levels of CRP, MMP-9, MMP-2, NT-proBNP and NE,the incidence of delirium, and the duration of weaning and ICU stay time between the two groups were observed and compared before and after treatment of 24 h. **Results:** There was no significant difference in CRP, MMP-9, MMP-2, NT-proBNP and NE levels between the two groups before treatment (P>0.05). The levels of CRP, MMP-9, MMP-2, NT-proBNP and NE in the study group were lower than those in the control group after treatment of 24 h, and the difference was statistically significant (P<0.05). The incidence of postoperative delirium in the study group was 7.14%(3/42), which was lower than 26.19% (11/42) of the control group (P<0.05). The duration of weaning and ICU stay in the study group were lower than those in the control group, the difference was statistically significant (P<0.05). **Conclusion:** Dexmedetomidine not only has analgesic and sedative effects, it also has a significant inhibitory effect on inflammatory response in patients with acute aortic dissection, and reduce the incidence of delirium, the prognosis quality of the patients is guaranteed.

Key words: Dexmedetomidine; Acute aortic dissection; Delirium; CRP; MMPs; NT-proBNP; NE

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前言

急性主动脉夹层是一种十分少见的危重心血管病变，是指主动脉壁中膜内血肿，具有发病急、死亡率高等特点[1,2]。据相关资料调查显示，欧美国家急性主动脉夹层的发病率约为 5~10/100 万，其中早期死亡率高达 60%[3]。因此，针对高度疑似

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急性主动脉夹层的患者,临床及时给予血流动力学指标调控与监测是非常必要,一旦确诊应立即采取手术治疗,保证患者的生命安全。然而,术后谵妄一直是急性主动脉夹层患者康复的主要并发症,越来越多的研究发现,炎性反应与急性主动脉夹层的发病、进展与预后具有密切的关系[4,5]。右美托咪啶属于α2高选择性肾上腺素能受体类药物,具有显著的镇痛与镇静作用[6,7]。目前,该药对急性主动脉夹层患者炎性反应、谵妄及血清指标影响的报道相对较少。为了进一步完善急性主动脉夹层的临床治疗方案,本研究通过对急性主动脉夹层患者应用右美托咪啶治疗,并分析该药对患者炎性反应、谵妄及血清基质金属蛋白酶(Matrix metalloproteinases, MMPs)、N 端前脑钠肽(N end forebrain natriuretic peptide, NT-proBNP)、中性粒细胞弹性蛋白酶(Neutrophil elastase, NE)水平的影响,现报道如下。

1 资料与方法

1.1 临床资料

选择我院于 2014 年 1 月至 2017 年 1 月期间收治的 84 例急性主动脉夹层患者,纳入标准:(1)经影像学检查证实;(2)伴有高血压、恐惧、焦虑、疼痛、谵妄的患者;(3)需使用镇静镇痛药物,且使用时间 >24 h;(4)本次研究内容已告知患者家属,并已取得其同意。排除标准:(1)左心室射血分数在 30%以下;(2)伴有重度窦性心动过缓、病窦综合征、血流动力学障碍、房室传导阻滞在 II 度及以上、严重脏器功能障碍;(3)近三个月内接受过其他镇定药物治疗者;(4)对本次研究药物过敏者。采用随机数字表法将所有患者分为对照组(n=42)与研究组(n=42)。其中对照组男 26 例,女 16 例;年龄 24~76 岁,平均(49.63± 5.64)岁;手术类型:主动脉根部替换联合孙氏手术 10 例,单纯升主动脉替换联合孙氏手术 20 例, 主动脉瓣成形术联合孙氏手术 7 例,升主动脉与主动脉瓣替换联合孙氏手术 5 例。研究组男 28 例,女 14 例;年龄 25~75 岁,平均(50.84± 5.51)岁;手术类型:主动脉根部替换联合孙氏手术 9 例,单纯升主动脉替换联合孙氏手术 19 例,主动脉瓣成形术联合孙氏手术 6 例,升主动脉与主动脉瓣替换联合孙氏手术 8 例。两组患者临床资料比较无差异(P>0.05)。我院伦理委员会已批准本次研究。

1.2 方法

对照组入院后给予吗啡(青海制药厂有限公司,国药准字:H63020013)镇痛,剂量为 0.2~0.6 mg/h;研究组则给予右美托咪啶(辰欣药业股份有限公司,国药准字:H20130027,规格:2 mL:0.2 mg)镇痛,剂量为 0.2~0.7 μg/kg/h。术后均进行肝肾功能、血常规、凝血功能、电解质、心电图、血气分析与床旁 X 胸片检查,并根据患者具体情况给予影像学与实验室等检查。

1.3 观察方法

(1) 观察对比两组治疗前与治疗 24 h 后炎症指标 C 反应蛋白(C reactive protein, CRP)、基质金属蛋白酶 -9(matrix metalloproteinases-9, MMP-9)、基质金属蛋白酶 -2(matrix metalloproteinases-2, MMP-2)、NT-proBNP、NE 水平的变化。于治疗前、治疗 24 h 后采集所有患者清晨空腹外周血 6 mL,以 3000 r/min 离心 8 min,离心半径 6 cm,取上清液,置于 -30℃温箱中待测。采用酶联免疫吸附法检测血清 CRP、MMP-9、MMP-2、NT-proBNP、NE,试剂盒(购自雅培生物科技有限公司),严格按照试剂盒说明书操作进行。(2)参照谵妄评估法[8],对比两组术后谵妄的发生率。① 注意力散漫;② 精神状态起伏不定或突然改变;③ 意识改变(完全清醒外的意识状态,例如昏睡、嗜睡、警醒或昏迷);④ 思维无序;具备① 与② ,且符合③ 或④ 中任意一项即为谵妄。(3)观察对比两组脱机持续时间与 ICU 入住时间。

1.4 统计学方法

本研究数据均采用 SPSS19.0 软件进行统计分析, 炎性指标等计量资料以($\bar{x}$± s)表示,采用 t 检验;谵妄发生率等计数资料以率(%)表示,采用 x^2 检验,P<0.05 为差异有统计学意义。

2 结果

2.1 两组患者炎性指标水平比较

两组患者治疗前 CRP、MMP-9、MMP-2、NT-proBNP 与 NE 水平比较差异无统计学意义 (P>0.05), 治疗 24 h 后, 研究组 CRP、MMP-9、MMP-2、NT-proBNP 与 NE 水平低于对照组与治疗前(P<0.05)。见表 1。

表 1 两组患者炎性指标水平比较($\bar{x}$± s)

Table 1 Comparison of inflammatory indexes between the two groups($\bar{x}$± s)

Groups	Time	CRP(mg/L)	MMP-9(ng/ml)	MMP-2(ng/ml)	NT-proBNP (pg/ml)	NE(ng/ml)
Study group(n=42)	Before treatment	120.52± 5.62	136.55± 50.63	115.21± 20.65	625.51± 80.62	230.55± 50.57
	After treatment of 24 h	65.43± 4.25[ab]	35.62± 15.25[ab]	55.61± 20.27[ab]	210.62± 30.53[ab]	182.02± 25.63[ab]
Control group (n=42)	Before treatment	120.63± 5.84	135.64± 50.68	114.88± 20.51	628.55± 78.62	230.85± 48.61
	After treatment of 24 h	98.61± 5.65	95.62± 40.31	74.31± 25.65	398.62± 40.54	198.6± 30.53

Note: compared with before treatment, [a]P<0.05; compared with the control group, [b]P<0.05.

2.2 两组患者术后谵妄的发生率比较

研究组有 3 例患者出现术后谵妄, 对照组有 11 例患者出现术后谵妄,研究组术后谵妄的发生率为 7.14%(3/42),低于对照组的 26.19%(11/42),差异有统计学意义(x^2=5.486,P<0.05)。

2.3 两组患者脱机持续时间与 ICU 入住时间比较

研究组脱机持续时间与 ICU 入住时间均少于对照组,差异有统计学意义(P<0.05)。见表 2。

3 讨论

急性主动脉夹层又可称为夹层血肿,是一种高危的心血管疾病,具有发病急、病情复杂、进展迅速等特点,若未及时采取有效的治疗措施,将严重危害患者的生命安全[9,10]。目前,急性

表 2 两组患者脱机持续时间与 ICU 入住时间比较(d, $\bar{x}\pm s$)

Table 2 Comparison of duration of weaning and ICU stay time between the two groups(d, $\bar{x}\pm s$)

Groups	n	Duration of weaning time	ICU stay time
Study group	42	1.33± 0.62	4.53± 1.22
Control group	42	2.95± 1.27	8.82± 2.03
t		4.021	5.682
P		0.000	0.000

主动脉夹层已成为急危重症治疗中最为棘手的疾病之一,同时也是临床学者研究的重点[11,12]。有研究发现,急性主动脉夹层的起病、进展及预后均与炎性反应有关[13]。CRP 属于急性主动脉夹层非特异性且敏感的炎症标记物,且是预防心血管风险与测定血管炎症的独立危险因子[14-16]。同时,急性主动脉夹层患者常常伴有心室舒张功能障碍、高血压等疾病,导致 NT-proBNP 升高,其指标与预后密切相关。MMPs 能够参与新生血管形成,并且可破坏降解弹性纤维,促使血管生成因子释放[17,18]。有研究指出,MMPs 与主动脉瘤、急性冠状动脉综合征与夹层介导的急性肺损伤有关,急性主动脉夹层炎性反应可以在一定程度上激活中性粒细胞,促使弹性蛋白酶释放并且损伤肺组织[19,20]。NE 是由心脏分泌的利尿钠肽家族一员,能够调节血容量与血压的自稳平衡,并具有利尿作用[21]。

右美托咪啶具有中枢性抗焦虑、抗交感等作用,且可以双相调节心血管系统[22]。同时,右美托咪啶能够直接激活血管平滑肌α2 受体,促使血管收缩,提高血压水平,反射性导致心动减缓;持续治疗可以减少交感神经紧张度,提高迷走神经冲动,继而降低血管舒张压水平。目前,关于右美托咪啶抗炎作用机制的研究不多,发挥抗炎的机制尚未完全阐明[23]。有研究指出,右美托咪啶通过激活中枢α2 肾上腺素能受体, 从而交感兴奋度受到抑制,继而胆碱能抗炎通路被激活,从而调节炎性因子表达水平 [24]。本研究结果显示, 研究组治疗 24 h 后 CRP、MMP-9、MMP-2、NT-proBNP 与 NE 水平低于对照组与治疗前(P<0.05)。可见,右美托咪定能够有效调节机体炎性因子水平,避免炎性反应所介导的急性脏器损伤, 改善患者的预后质量,这可能与α2 肾上腺素能受体信号转导通路被激活, 免疫细胞相关炎症反应得到了有效抑制有关[25]。目前研究发现,术后谵妄一直是影响急性主动脉夹层患者康复的主要并发症,但其发生机制仍未完全明确[26]。急性主动脉夹层患者受疼痛、恐惧、焦虑与睡眠障碍等原因的影响极易并发谵妄症状,而躁动型谵妄可增加夹层破裂的风险[27]。有学者研究指出,右美托咪定对脂多糖所致的活化小神经胶质细胞炎症反应具有抑制作用,可以作为谵妄的有效药物[28]。研究组术后谵妄的发生率为 7.14%,低于对照组的 26.19%(P<0.05),可见,相较于传统吗啡,右美托咪啶对急性主动脉夹层患者谵妄的预防效果更为理想。这可能与两种药物的药理作用机制有关。吗啡是通过激活中枢神经系统阿片受体而产生强大的镇痛作用,与吗啡相比,右美托咪啶具有中枢性抗交感、焦虑等作用,镇静效果较好,且对呼吸无抑制作用。因此右美托咪啶谵妄的发生率较低。此外,研究组脱机持续时间与 ICU 入住时间均低于对照组。右美托咪啶能够有效保证急性主动脉夹层患者的恢复效果, 进一步缩短康复速度,这与部分报道结果相符[29,30]。

综上所述,右美托咪啶治疗急性主动脉夹层患者,疗效满意,可有效抑制炎性反应,降低炎症因子水平,术后谵妄发生率明显降低,利于患者预后,值得临床推广应用。

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