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盐酸右美托咪定联合乌司他丁对老年腹部手术患者术后认知功能障碍的影响分析*

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摘要 目的:探讨盐酸右美托咪定联合乌司他丁对老年腹部手术患者术后认知功能障碍的影响及可能机制。**方法:**选择 2018 年 1 月到 2018 年 6 月在我院胃肠外科、泌尿外科、肝胆外科行开腹手术的 150 例患者为研究对象,按照数字表随机分为右美托咪定组、乌司他丁组和联合组,每组各 50 例患者。比较三组患者的术后苏醒时间、有效镇痛时间、躁动例数及术后认知功能障碍(POCD)的发生情况,治疗前后血清肿瘤坏死因子 α (TNF- α)、白介素 6(IL-6)、血清 S-100 蛋白(S100 β)水平、简易智能状态量表(MMSE)评分的变化及不良反应的发生情况。**结果:**三组患者麻醉苏醒时间比较差异无统计学意义($P>0.05$);联合组患者苏醒期躁动及 POCD 发生率明显低于右美托咪定组及乌司他丁组,有效镇痛时间明显长于右美托咪定组及乌司他丁组($P<0.05$);治疗后,三组患者血清 TNF- α 、IL-6 及 S100 β 水平均较治疗前明显改善,且联合组患者各个时点血清 TNF- α 、IL-6 及 S100 β 水平均明显低于右美托咪定组及乌司他丁组($P<0.05$)。联合组 MMSE 评分明显高于右美托咪定组及乌司他丁组($P<0.05$)。联合组不良反应总发生率为 24.00%,显著低于右美托咪定组(50.00%)和乌司他丁组(48.00%)($P<0.05$)。**结论:**与单用盐酸右美托咪定和乌司他丁相比,盐酸右美托咪定联合乌司他丁可更有效预防老年腹部手术患者苏醒躁动及 POCD 的发生,且安全性更高,可能与其明显降低患者血清炎症因子水平有关。

关键词:盐酸右美托咪定;乌司他丁;老年腹部手术;炎症因子;认知功能障碍

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Analysis of the Efficacy of Dexmedetomidine hydrochloride combined with Ulinastatin in the Treatment of Cognitive Dysfunction in the Elderly Patients with Abdominal Surgery*

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ABSTRACT Objective: To investigate the effect of dexmedetomidine hydrochloride combined with ulinastatin on the postoperative inflammatory factors and cognitive dysfunction in the elderly patients undergoing abdominal surgery and its possible mechanisms. **Methods:** 150 cases of patients who underwent open surgery in the gastroenterology, urology and hepatobiliary surgery of our hospital from January 2018 to June 2018 were selected and divided into the dexmedetomidine group, the ulinastatin group and the combined group according to the randomized regimen, with 50 patients in each group. The postoperative recovery time, effective analgesia time, number of agitation cases and postoperative cognitive dysfunction (POCD), changes of serum tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6) and S-100 protein (S100 β) levels, simple intelligent state scale (MMSE) score before and after treatment and the occurrence of adverse reactions were compared between the three groups. **Results:** There was no significant difference in the recovery time of anesthesia among the three groups ($P>0.05$). The incidence of restlessness and POCD in the combined group was significantly lower than that in the dexmedetomidine group and the ulinastatin group, and the effective analgesia time was significantly longer than that of the dexmedetomidine group and the ulinastatin group($P<0.05$). After treatment, the levels of TNF-alpha, IL-6 and S100beta levels in the three groups were significantly improved compared with those before treatment, and the levels of TNF-alpha, IL-6 and S100beta in the combined group were significantly lower than those in dexmedetomidine group and ulinastatin group at all time points ($P<0.05$). After treatment, the MMSE score of the combined group was significantly higher than that of the dexmedetomidine group and the Ulinastatin group($P<0.05$).

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The total incidence of adverse reactions in combination group was 24.00%, significantly lower than that in dexmedetomidine group (50.00%) and ulinastatin group (48.00%)($P<0.05$). **Conclusion:** Compared with dexmedetomidine hydrochloride and ulinastatin alone, dexmedetomidine hydrochloride combined with ulinastatin can more effectively prevent the emergence of restlessness and POCD in the elderly patients undergoing abdominal surgery with higher safety, which may be related to its significant reduction of serum inflammatory factors.

Key words: Dexmedetomidine hydrochloride; Ulinastatin; Senile abdominal surgery; Inflammatory cytokines; Cognitive dysfunction

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前言

我国目前已经进入老龄化社会,老年腹部手术患者众多,认知功能障碍老年人术后常见的中枢神经系统并发症,临床表现为精神错乱、认知功能异常、记忆缺损,人格的改变等症状,严重时可能出现老年性痴呆,严重影响患者的生活质量^[1,2]。右美托咪定是一种 α_2 肾上腺素能受体激动剂,在镇静、抗焦虑方面具有良好的效果,既往常采用该药治疗老年患者术后认知功能障碍^[3,4]。乌司他丁属于蛋白酶抑制剂,常应用于心脏外科和胰腺炎的手术,能够抑制粒细胞弹性蛋白酶、巯基酶、纤溶酶等多种酶,同时还能清除自由基,改善免疫功能下降等作用^[5,6]。研究显示乌司他丁能有效减少老年腹部手术后认知功能障碍的发生^[7,8]。本研究主要探讨了盐酸右美托咪定联合乌司他丁对老年腹部手术患者的疗效,现将结果报道如下。

1 资料与方法

1.1 一般资料

选择2018年1月~2018年6月在我院胃肠外科、泌尿外科、肝胆外科行开腹手术的150例患者进行研究,研究已获得我院伦理会批准实施,所有受试者家属均签署知情同意书。采用简单随机分组法将其分为三组,联合治疗组男28例,女22例,年龄64~85岁,平均(74.78 $\pm$ 2.87)岁;右美托咪定组男29例,女21例,年龄66~86岁。平均(75.21 $\pm$ 2.69)岁;乌司他丁组男24例,女26例,年龄63~85岁。平均(76.17 $\pm$ 3.75)岁。三组患者性别($\chi^2=1.127, P=0.569$)、年龄($t=2.572, P=0.080$)等一般临床资料比较差异无统计学意义($P>0.05$),具有可比性。

纳入标准:(1)年龄 ≥ 65 岁;(2)文化程度均在小学及以上,能够配合本次研究;(3)术前无神经系统疾病史或药物滥用史;(4)肝、肾功能无明显异常,无心血管、呼吸系统重大疾病。排除标准:(1)有中枢神经系统疾病,服用抗抑郁药等;(2)有严重视

听说功能障碍者、老年痴呆以及药物依赖者;(3)有心血管、呼吸系统等重大手术史者。(4)有本研究药物禁忌症的患者。

1.2 治疗方法

右美托咪定组在麻醉诱导前采用0.5 μ g/kg(规格2mL:0.2mg,厂家:四川国瑞药业有限责任公司,国药准字H-20110097)微量泵注,手术结束前30min停止输注;乌司他丁组同样时间给予乌司他丁(规格1mL,厂家:广东天普生化医药股份有限公司,国药准字H19990133)2ku/kg;联合组按上述两种方法同时给予盐酸右美托咪定和乌司他丁持续泵注。

1.3 观察指标

(1)术后认知障碍发生率:患者于手术前和术后1d,3d,6d和14d采用MMSE进行认知能力检测。(2)术前(T0)、术毕(T1)、术后3h(T2)、术后1d(T3)、术后3d(T4)5个时间点抽取静脉血3mL,立刻离心(4000r/min,10min),提取上层血清后,置于零下20℃的冷冻箱内存储以备检测。血清S100 β 、IL-6、TNF- α 采用酶联免疫吸附法进行测定,试剂盒采用上海信裕生物科技有限公司生产人免疫球蛋白E(IgE)检测试剂盒,测定步骤严格按试剂盒操作说明进行。

1.4 统计学分析

以SPSS18.0软件包处理数据,计量资料均为正态分布,用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,组间比较使用独立样本t检验,多组比较采用方差分析,不同时间点采用重复测量方差分析,计数资料以率表示,组间比较采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 三组患者术后情况的比较

联合组患者苏醒期躁动及POCD的发生率明显低于右美托咪定组及乌司他丁组,有效镇痛时间明显长于右美托咪定组及乌司他丁组($P<0.05$),详见表1。

表1 三组术后苏醒时间、有效镇痛时间、躁动及POCD发生情况比较

Table 1 Comparison of the postoperative recovery time, effective analgesia time, incidence of agitation and POCD among the three groups

Groups	n	Wake up of time(min)	Number of agitation of awakening	Effective analgesic time(h)	POCD
Joint group	50	10.23 $\pm$ 4.15	1(2.00)	39.14 $\pm$ 3.53	3(6.00)
Dexmedetomidine group	50	10.19 $\pm$ 3.24	8(16.00)	7.37 $\pm$ 1.26	11(22.00)
Ulinastatin group	50	10.56 $\pm$ 3.68	9(18.00)	12.24 $\pm$ 3.64	12(24.00)
t		0.150	7.197	1608.775	6.793
P value		0.861	0.027	0.000	0.033

2.2 三组患者手术前后血清 TNF- α 、IL-6 及 S100 β 水平比较

术毕, 三组患者血清 TNF- α 、IL-6 及 S100 β 水平均较治疗前显著升高, 术后 3h、1d 和 3d, 三组患者血清 TNF- α 、IL-6 及

S100 β 水平逐渐降低, 且联合组患者各个时点血清 TNF- α 、IL-6 及 S100 β 水平均明显低于右美托咪定组及乌司他丁组($P<0.05$), 详见表 2。

表 2 三组患者手术前后血清 TNF- α 、IL-6 及 S100 β 水平的比较($\bar{x} \pm s$)Table 2 Comparison of the serum TNF- α , IL-6 and S100 levels before and after surgery among the three groups($\bar{x} \pm s$)

Groups	n	TNF- α (pg/mL)					IL-6(pg/mL)				
		T0	T1	T2	T3	T4	T0	T1	T2	T3	T4
Joint group	50	134.22 $\pm$ 35.47	146.31 $\pm$ 32.16	131.52 $\pm$ 25.34	118.37 $\pm$ 19.67	98.24 $\pm$ 35.68	448.90 $\pm$ 93.73	511.23 $\pm$ 103.24	487.49 $\pm$ 97.68	468.76 $\pm$ 96.75	445.56 $\pm$ 95.68
		135.18 $\pm$ 36.12	153.73 $\pm$ 32.17	146.47 $\pm$ 26.37	127.48 $\pm$ 18.73	108.78 $\pm$ 38.75	451.35 $\pm$ 95.37	528.34 $\pm$ 94.43	516.37 $\pm$ 96.37	507.34 $\pm$ 91.37	493.47 $\pm$ 89.67
Dexmedetomidine	50	135.37 $\pm$ 36.48	157.62 $\pm$ 33.21	143.34 $\pm$ 26.14	129.34 $\pm$ 18.64	110.34 $\pm$ 38.76	449.54 $\pm$ 96.58	527.64 $\pm$ 95.34	519.53 $\pm$ 95.76	503.58 $\pm$ 90.97	491.57 $\pm$ 88.63
Between groups		F=9.674, $P=0.000$					F=14.935, $P=0.000$				
Different time points		F=16.846, $P=0.000$					F=24.359, $P=0.000$				
Between groups, at different times		F=7.358, $P=0.000$					F=11.489, $P=0.000$				
Groups	n	S100 β (ng/mL)									
		T0	T1	T2	T3	T4					
Joint group	50	0.59 $\pm$ 0.04	0.73 $\pm$ 0.05	0.77 $\pm$ 0.05	0.89 $\pm$ 0.05	0.64 $\pm$ 0.03					
Dexmedetomidine	50	0.61 $\pm$ 0.05	0.87 $\pm$ 0.03	0.89 $\pm$ 0.09	1.08 $\pm$ 0.15	0.78 $\pm$ 0.05					
Ulinastatin	50	0.61 $\pm$ 0.04	0.86 $\pm$ 0.04	0.83 $\pm$ 0.07	1.04 $\pm$ 0.16	0.81 $\pm$ 0.05					
Between groups		F=7.684, $P=0.000$									
Different time points		F=15.348, $P=0.000$									
Between groups, at different times		F=6.347, $P=0.000$									

2.3 三组手术前后 MMSE 评分的比较

三组治疗前 MMSE 评分比较差异无统计学意义($P>0.05$);

治疗后, 联合组 MMSE 评分明显高于右美托咪定组及乌司他丁组, 差异具有统计学意义($P<0.05$), 详见表 3。

表 3 三组手术前后 MMSE 评分的比较($\bar{x} \pm s$)Table 3 Comparison of the MMSE score before and after surgery among three groups($\bar{x} \pm s$)

Groups	n	MMSE score		
		Preoperation	At 1 day postoperation	At 7 days postoperation
Joint group	50	26.64 $\pm$ 2.51	26.34 $\pm$ 2.94	26.57 $\pm$ 6.67
Dexmedetomidine group	50	26.59 $\pm$ 2.58	23.21 $\pm$ 5.42	24.57 $\pm$ 5.23
Ulinastatin group	50	26.51 $\pm$ 2.47	23.11 $\pm$ 3.47	23.87 $\pm$ 2.49
Between groups		F=8.904, $P=0.000$		
Different time points		F=14.268, $P=0.000$		
Between groups, at different times		F=7.348, $P=0.000$		

2.4 三组患者不良反应发生情况的比较

三组不良反应总发生率分别为 24.00%、50.00%、48.00%, 联合组显著低于右美托咪定组及乌司他丁组, 差异具有统计学意义($P<0.05$), 见表 4。

3 讨论

POCD 是指患者受围术期各种因素的影响, 术后出现大脑功能紊乱, 临床表现为认知、意志的改变及记忆力受损, 是属于

可逆的及具有波动性的急性精神紊乱^[9,10]。随着老年化社会的到来,术后认知功能障碍的发生也随之升高。因此,减少围手术期 POCD 的发生对提高老年患者的生活质量具有重要意义^[11,12]。

目前,术后 POCD 以预防为主,多采用围手术期的术前准备改善手术中的麻醉管理^[13,14]。一旦发生精神障碍,建议围手术期尽早进行合理的治疗和药物干预治疗等措施进行预防^[15,16]。

表 4 三组患者不良反应发生情况的比较[例(%)]

Table 4 Comparison of the incidence of adverse reactions among three groups[n(%)]

Groups	n	Nausea and vomiting	Restlessness	Bradycardia	High blood pressure	The total incidence of
Joint group	50	1(2.00)	3(6.00)	6(12.00)	2(4.00)	12(24.00)
Dexmedetomidine group	50	4(8.00)	7(14.00)	9(28.00)	5(10.00)	25(50.00)
Ulinastatin group	50	5(10.00)	6(12.00)	7(14.00)	6(12.00)	24(48.00)
χ^2 value		2.786	1.819	0.746	2.790	8.676
P value		0.248	0.403	0.689	0.335	0.013

有研究显示 $\alpha 2$ -肾上腺素受体激动剂能激动剂可抑制中枢交感神经系统,调节免疫系统,减少炎症反应,激活抗凋亡,从而保护其大脑、肝脏等多种脏器的受损细胞^[17,18]。右美托咪定能通过抑制其炎症反应减少术后 POCD 的发生^[19,20]。而乌司他丁是一种单链多肽糖蛋白,能够通过抑制炎症因子、清除自由基等方式减轻器官的炎症损伤^[21,22]。本研究结果显示盐酸右美托咪定联合乌司他丁治疗的患者的苏醒期躁动及 POCD 的发生率明显低于单独使用右美托咪定及乌司他丁治疗的患者,而有效镇痛时间明显高于单独使用右美托咪定及乌司他丁治疗的患者,提示联合用药在手术中效果较好,能显著预防 POCD 的发生。分析是因为乌司他丁能够减轻患者脑缺血再灌注损伤和神经元凋亡,而盐酸右美托咪定用于术后辅助麻醉,能保护患者的中枢神经,两者联用改善患者的认知功能。

TNF- α 是具有肿瘤杀伤作用的生物活性因子之一,能够启动机体的炎症反应^[23,24]。IL-6 由多种细胞合成,可促进 B 细胞增殖、分化并产生抗体,其水平的变化可以反映组织损伤的程度^[25-27]。S100 β 是反映中枢神经系统损伤的特异性标志,主要存在于施万细胞和星形胶质细胞中,当中枢神经系统发生损伤时可进入脑脊液,然后通过血脑屏障进入血液^[28-30]。研究结果显示联合治疗的患者血清 TNF- α 、IL-6、S100 β 水平明显低于使用单药治疗组,且 MMSE 评分明显高于右美托咪定组及乌司他丁组。分析原因是因为右美托咪定可以通过抑制机体应激反应来降低术后患者的儿茶酚胺和炎症因子;而乌司他丁则能通过抑制促炎性细胞因子释放来发挥脑保护作用,最终改善患者的炎症因子水平。此外,联合用药的患者的不良反应的发生率明显低于单用右美托咪定和乌司他丁治疗,提示联合用药效果好,安全性高。

综上所述,与单用盐酸右美托咪定和乌司他丁相比,盐酸右美托咪定联合乌司他丁可更有效预防老年腹部手术患者苏醒躁动及 POCD 的发生,且安全性更高,可能与其明显降低患者血清炎症因子水平有关。

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