·临床研究·

不同剂量右美托咪定对老年患者内镜逆行胰胆管造影术后认知功能的影响

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【摘 要】 目的 观察不同剂量右美托咪定对老年患者行内镜逆行胰胆管造影(ERCP)术后认知功能的影响。**方法** 入选2014年5月至2015年1月北部战区总医院麻醉科择期行ERCP的老年患者(≥65岁)120例,随机数表法将患者分为对照组(C组)、0.5 μg右美托咪定组(D1组)和0.8 μg右美托咪定组(D2组),每组40例。右美托咪定组均于麻醉诱导前给予右美托咪定1.0 μg/kg的负荷量,输注时间10 min,然后分别持续输注0.5 μg/(kg·h)和0.8 μg/(kg·h)至手术结束,C组输注等容积的生理盐水。记录患者一般情况、术中用药量、不良反应发生率,并分别于术前(Ta)、术毕即刻(Tb)、术后24 h(Tc)采集患者静脉血,用ELISA法检测血浆中白细胞介素-6(IL-6)、肿瘤坏死因子-α(TNF-α)及S-100β蛋白水平。于术前第1天、术后第1天和第3天用成人简易智能精神状态检查(MMSE)量表评估患者是否发生认知功能障碍(POCD)。采用SPSS 19.0统计软件对数据进行分析。组间比较采用方差分析或χ^2检验。**结果** 与C组比较,D1组和D2组患者丙泊酚用量[(112.84±40.10) *vs* (182.01±61.88) mg;(100.96±46.64) *vs* (182.01±61.88) mg]减少,差异均有统计学意义($P<0.05$);D1组和D2组患者Tb和Tc时IL-6、TNF-α和S-100β蛋白水平均降低,且差异均有统计学意义($P<0.05$)。3组患者体动、呃逆及呼吸抑制发生率差异均有统计学意义($P<0.05$)。D1和D2组患者术后各1例发生POCD,发生率均为2.5%(1/40),C组患者术后共8例发生POCD,发生率为20.0%(8/40),差异有统计学意义($P=0.005$)。**结论** 老年人ERCP术中应用右美托咪定可减少丙泊酚用量和不良反应,降低POCD的发生率。

【关键词】 老年人;内镜逆行胰胆管造影术;右美托咪定;认知功能障碍
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Effects of different doses of dexmedetomidine on postoperative cognitive function in elderly after endoscopic retrograde cholangiopancreatography

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【Abstract】 Objective To investigate the effect of different doses of dexmedetomidine on cognitive function in elderly patients after endoscopic retrograde cholangiopancreatography (ERCP). **Methods** A total of 120 elderly patients (≥65 years old) undergoing elective ERCP in the General Hospital of Northern Theater Command from May 2014 to January 2015 were recruited in this study. They were randomly divided into control group (group C), 0.5 μg (group D1) and 0.8 μg dexmedetomidine group (group D2), with 40 cases in each group. Dexmedetomidine of 1.0 μg/kg were infused before induction to the patients of the latter 2 groups as loading dose for 10 min, and then were given at 0.5 μg/(kg·h) (group D1) or 0.8 μg/(kg·h) (group D2) by continued infusion until the end of surgery. The group C was infused with the same volume of normal saline. The clinical data, such as general condition, intraoperative dosage of propofol, and incidences of adverse reactions were recorded. Venous blood samples were collected to detect the levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and soluble protein 100-β (S-100β) by ELISA before operation (Ta), immediately after operation (Tb), and 24 h after operation (Tc). Mini-mental state examination (MMSE) was perfermed to test the occurrence of postoperative cognitive dysfunction (POCD) at 1 d before, 1 d and 3 d after operation. The data was analyzed by using SPSS statistics 19.0. Comparison among groups was performed by analysis of variance or Chi-square test. **Results** Compared

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with group C [(182.01±61.88) mg], the dosage of propofol was significantly lower in group D1 [(112.84±40.10) mg] and group D2 [(100.96±46.64) mg], both with significant difference ($P<0.05$). The plasma levels of TNF-α, IL-6 and S-100β were also obviously lower in group D1 and group D2 at Tb and Tc when compared with group C (all $P<0.05$). Statistical differences were seen in the incidences of body movement, hiccups and respiratory depression among the 3 groups ($P<0.05$). After operation there was 1 patient suffering from POCD in group D1, with the incidence rate of 2.5%, so was in group D2, and the rate was significantly lower than that of group C (8 cases, 20.0%, $P=0.005$). **Conclusion** Intraoperative infusion of dexmedetomidine can reduce the dosage of propofol and prevent adverse reactions in the elderly undergoing ERCP, and decrease the occurrence of POCD at the same time.

【Key words】 aged; endoscopic retrograde cholangiopancreatography; dexmedetomidine; cognitive dysfunction

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术后认知功能障碍(postoperative cognitive dysfunction,POCD)是老年患者手术后常见的一种并发症,可延长患者住院时间,增加医疗费用,给生活带来严重不良影响。研究表明,老年患者全麻后 1 周内 POCD 的发生率高达 25.8%[1]。而老年人胆胰疾病发病率是年轻人的 4 倍,内镜逆行胰胆管造影术(endoscopic retrograde cholangiopancreatography,ERCP)已广泛被用于老年胆胰疾病患者[2]。ERCP 一般采取不进行气管插管的监测麻醉(monitored anesthesia care,MAC),因此要求一定的镇静镇痛及制动深度。本课题组前期对比了右美托咪定与瑞芬太尼在 ERCP 手术中的应用,证实右美托咪定可很好地用于 ERCP 手术,并减少呼吸抑制的发生。研究表明右美托咪定能在降低患者应激反应的同时,减少炎症因子的释放[3],降低脑卒中老年患者术后谵妄发生率[4],为此本研究观察了右美托咪定对老年患者行 ERCP 术后 POCD 的影响,并检测患者血浆中肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)、白细胞介素-6(interleukin-6,IL-6)以及可溶性蛋白-100β(soluble protein 100-β,S-100β)水平变化,探讨其可能的发生机制。

1 对象与方法

1.1 研究对象

入选 2014 年 5 月至 2015 年 1 月北部战区总医院麻醉科择期行 ERCP 的老年患者 120 例,随机数表法将患者分为对照组(C 组)、0.5 μg 右美托咪定组(D1 组)和 0.8 μg 右美托咪定组(D2 组),每组 40 例。纳入标准:美国麻醉医师协会(American Society of Anesthesiologists,ASA)Ⅱ~Ⅲ级;年龄≥65 岁;既往无明确诊断的心肺病史;既往无脑卒中、脑外伤及脑部手术史;术前成人简易智能精神状态检查(mini-mental state examination,MMSE)量表评分≥23 分;既往无明确诊断的心理疾病、抑郁症等;空腹血糖<7.0 mmol/L;手术时间<60 min。排除标准:既往有明确诊断的恶性高血压、冠心病、严重心律失常及心功能不全;有颅脑外伤及神经系统疾病;有明显的精神疾病及服用抗精神病药物史;体质量指数>25 kg/m^2 或者<18.5 kg/m^2;围手术期发生不良事件(大出血、呼吸暂停、心脑血管意外);术中发生意外死亡;各种原因致实验不能严格按照要求正常进行;手术时间>60 min;中途患者及家属要求终止实验;术后拒绝随访。本研究经医院伦理委员会同意,并与患者及家属签署知情同意书。

1.2 麻醉方法

患者术前常规禁食 8 h,禁饮 4 h,入室后监测心率(heart rate,HR)、心电图(electrocardiogram,ECG)、脉搏血氧饱和度(pulse oxygen saturation,SpO_2)等生命体征。建立静脉通路,局部麻醉下右桡动脉穿刺置管监测有创动脉血压,采动脉血查血气及电解质,然后常规经特制的可行气体采集的鼻导管吸氧 3 L/min,监测脑电双频谱指数(bispectral index,BIS)。D1 组和 D2 组患者麻醉诱导前给予右美托咪定 1.0 μg/kg,输注时间 10 min;诱导时给予舒芬太尼 0.1 μg/kg、丙泊酚 1 mg/kg 缓慢静脉推注。维持时 D1 组每小时给予右美托咪定 0.5 μg/kg,丙泊酚 2~5 mg/kg;D2 组每小时给予右美托咪定 0.8 μg/kg,丙泊酚 2~5 mg/kg。C 组麻醉诱导前给予相同容积的生理盐水;诱导时给予舒芬太尼 0.1 μg/kg、丙泊酚 1 mg/kg 缓慢静脉推注;维持时每小时给予丙泊酚 2~5 mg/kg。BIS 维持在 40~60。严密监测患者术中生命体征变化,当血压下降>30%时,给予麻黄碱 10 mg 提升血压,HR<45 次/min 时静脉推注阿托品 0.3 mg 提升 HR。呼气末二氧化碳(end tidal carbon dioxide,$ETCO_2$)维持在 35~45 mmHg(1 mmHg=0.133 kPa),维持 SpO_2>90%。根据术中体动变化及时推注丙泊酚,每次 0.5 mg/kg。SpO_2<90%、$ETCO_2$>45 mmHg、呼吸频率(respiratory rate,RR)<8 次/min 转为面罩吸氧,直至 SpO_2>95%。手术结束时给予昂丹司琼 8 mg、氟比洛芬酯 50 mg 防

止苏醒期躁动、恶心和呕吐发生。

1.3 观察指标

分别于手术前即刻(Ta)、手术结束后即刻(Tb)、术后24 h(Tc)3个时间点抽取静脉血2 ml置于乙二胺四乙酸(disodium ethylenediamine tetraacetic acid,EDTA)真空抗凝管中,-20℃冰箱保存,采用酶联免疫吸附法(enzyme-linked immunosorbent assay,ELISA)检测血浆中IL-6、TNF-α及S-100β水平。神经精神功能测定:分别于术前1 d(T1)、术后1 d(T2)和术后3 d(T3)用MMSE量表评估患者认知功能。MMSE评分低于基础值2分认为发生POCD[5,6]。

1.4 统计学处理

采用SPSS 19.0统计软件对数据进行分析。计量资料用均数±标准差($\bar{x}\pm s$)表示,组间比较采用方差分析。计数资料用例数(百分率)表示,组间比较用χ^2检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 3组患者基线资料比较

相比C组,D1组和D2组患者麻醉维持中丙泊酚用药量减少,且差异有统计学意义($P<0.05$)。3组患者的其他临床资料差异无统计学意义($P>0.05$;表1)。

2.2 3组患者IL-6、TNF-α和S-100β蛋白水平比较

相比Ta,3组患者Tb和Tc时IL-6、TNF-α和S-100β蛋白水平均明显升高,且差异均有统计学意义($P<0.05$)。相比C组,D1组和D2组Tb和Tc时IL-6、TNF-α和S-100β蛋白水平降低,且差异均有统计学意义($P<0.05$;表2)。

2.3 3组患者不良反应发生率比较

3组患者体动、呃逆及呼吸抑制发生率差异均有统计学意义($P<0.05$;表3)。

表1 3组患者基线资料比较

Table 1 Comparison of baseline data among three groups ($n=40$)

Item	Group D1	Group D2	Group C	F/χ^2	P value
Gender(male/female, n)	17/23	20/20	22/18	1.267	0.531
Age(years, $\bar{x}\pm s$)	76.3±11.1	76.1±12.8	75.3±10.1	0.168	0.846
Height(cm, $\bar{x}\pm s$)	167.41±8.59	166.55±9.15	166.70±9.42	0.923	0.400
Body mass(kg, $\bar{x}\pm s$)	60.51±6.14	59.80±6.35	59.90±7.04	0.202	0.817
BMI(kg/m^2, $\bar{x}\pm s$)	21.61±2.66	21.36±2.57	21.09±2.75	0.146	0.864
ASA(Ⅱ/Ⅲ, n)	16/24	14/26	18/22	0.833	0.659
Dosage of propofol(mg, $\bar{x}\pm s$)	112.84±40.10	100.96±46.64	182.01±61.88	4.133	0.018
Duration of operation(min, $\bar{x}\pm s$)	29.89±3.56	31.48±1.05	30.59±2.87	1.036	0.358
Duration of recovery(min, $\bar{x}\pm s$)	4.38±1.15	4.78±0.07	3.46±0.89	1.542	0.218
Length of staying in operating room(min, $\bar{x}\pm s$)	51.74±0.99	55.38±1.68	53.43±2.18	1.043	0.356
MMSE before operation(score, $\bar{x}\pm s$)	29.05±0.75	29.10±0.71	29.00±0.78	0.179	0.837

D1: 0.5 μg/(kg·h) dexmedetomidine; D2: 0.8 μg/(kg·h) dexmedetomidine; C: control; BMI: body mass index; ASA: American Society of Anesthesiologists; MMSE: mini-mental state examination.

表2 3组患者不同时间点IL-6、TNF-α and S-100β水平比较

Table 2 Comparison of levels of IL-6, TNF-α and S-100β at different time points among three groups ($n=40$, pg/ml, $\bar{x}\pm s$)

Item	Group	Ta	Tb	Tc
IL-6	D1	3.05±1.24	4.11±1.63*#	6.39±4.11*#
	D2	2.93±0.95	4.21±2.56*#	13.44±18.21*#
	C	3.24±1.97	6.26±4.90*	25.43±33.30*
TNF-α	D1	7.82±3.37	8.38±3.48*#	8.17±2.08*#
	D2	6.48±2.72	7.17±3.64*#	7.03±2.19*#
	C	7.77±2.71	9.17±3.75*	9.02±4.41*
S-100β	D1	1 009.45±308.25	1 312.46±233.51*#	1 411.37±234.26*#
	D2	1 007.26±305.35	1 310.82±230.49*#	1 409.63±231.58*#
	C	1 024.43±331.19	1 699.20±376.32*	1 798.01±377.47*

D1: 0.5 μg/(kg·h) dexmedetomidine; D2: 0.8 μg/(kg·h) dexmedetomidine; C: control; Ta: preoperation; Tb: immediately after operation; Tc: 24 h after operation; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; S-100β: soluble protein-100β. Compared with Ta, *$P<0.05$; compared with group C, #$P<0.05$.

表 3 3 组患者不良反应发生率比较

Table 3 Comparison of incidence of adverse reactions among three groups [n=40, n(%)]

Group	Body movement	Hiccups	Respiratory depression
D1	3(7.5)	1(2.5)	0(0)
D2	2(5.0)	1(2.5)	0(0)
C	9(22.5)	6(15.0)	6(15)
χ^2	6.954	6.696	12.632
P value	0.031	0.035	0.002

D1: 0.5 μg/(kg·h) dexmedetomidine; D2: 0.8 μg/(kg·h) dexmedetomidine; C: control.

2.4 3 组患者 POCD 发生率比较

D1 和 D2 组患者术后 1 d 时 1 例发生 POCD,发生率均为 2.5%(1/40),C 组患者术后共 8 例发生 POCD,分别发生在术后 1 d 和术后 3 d, 发生率为 20.0%(8/40),差异有统计学意义(P=0.005)。

3 讨 论

POCD 是老年人在接受手术后较常发生的一种并发症,常见临床表现有烦躁不安、记忆受损、社交能力下降等,属于轻度认知功能障碍[7],近期可出现精神恍惚、语无伦次、记忆力丧失,而远期则可表现为社交能力丧失、生活不能自理,严重者发展成阿尔兹海默病,给家庭和社会增加负担[8]。

右美托咪定是一种新型高选择性 α2 肾上腺素受体激动药,分布半衰期约 6 min,消除半衰期 2 h,除了镇静、镇痛外,具有可唤醒特点,因此可控性更强。既往研究表明右美托咪定可减少麻醉诱导期硫喷妥钠及维持期芬太尼用量[9]。本研究对象所使用的药物种类、批号均无差别,因此术中丙泊酚用量多少与是否使用右美托咪定有关。术中 BIS 值 40~60,麻醉深度基本靠调节丙泊酚用量维持,C 组丙泊酚用量(182.01±61.88) mg,而研究组用量分别为(112.84±40.10) mg 和(100.96±46.64) mg,差异有统计学意义,进一步证明右美托咪定可减少围手术期镇静药物的使用剂量。Kanda 等[10]把右美托咪定应用在心脏手术中,结果证明丙泊酚用量比对照组用量减少,本研究结果与其相符。右美托咪定镇静过程中无呼吸抑制作用,且具有镇痛作用,因此可有效降低 ERCP 手术刺激所致不适,从而降低不良反应的发生。

研究表明手术所致组织损伤可激活外周固有免疫系统,促进机体释放炎症介质,而外周炎症因子可通过血脑屏障进入中枢神经系统,或通过激活血脑屏障内神经内分泌细胞来合成并释放炎症因子,造成中枢炎症反应,进而干扰神经元活动,扰乱突触间的联系和信号传导,诱发 POCD[11]。目前 IL-6 和 TNF-α 被认为是最典型的促炎细胞因子,并且促炎反应在手术创伤时被延长。右美托咪定可减轻脂多糖引起的炎症反应,降低死亡率,并可降低患者 TNF-α 和 IL-6 水平[12,13]。右美托咪定可通过 Toll 样受体/核因子(nuclear factor-κB,NF-κB)途径及烟碱型乙酰胆碱受体 α7 抑制炎症[14,15]。本研究结果表明,与 Ta 时比较,Tb 和 Tc 时 3 组患者 IL-6 和 TNF-α 水平均明显升高,且差异均有统计学意义,可见 ERCP 术可促进机体促炎细胞因子释放。Tb 和 Tc 时,D1 组和 D2 组 IL-6 和 TNF-α 水平均低于 C 组,且差异均有统计学意义,表明老年患者 ERCP 中应用右美托咪定可一定程度降低手术结束时和术后 IL-6 和 TNF-α 水平,减轻炎症反应。S-100β 蛋白是一种酸性钙离子结合蛋白,极易通过血脑屏障,可反映早期脑受损程度,在神经系统疾病中发挥重要作用,还可评估全麻后 POCD 概率[16,17]。与 Ta 时比较,Tb 和 Tc 时 3 组患者 S-100β 蛋白水平均明显升高,且差异均有统计学意义,表明 ERCP 术可诱发脑功能受损。Tb 和 Tc 时,D1 组和 D2 组 S-100β 蛋白水平均低于 C 组,且差异均有统计学意义。这表明老年患者 ERCP 中应用右美托咪定可一定程度降低术后 S-100β 蛋白水平,减轻脑损伤和降低 POCD 发生率,其机制可能与其降低炎性因子水平相关。

综上,老年患者 ERCP 术中应用右美托咪定不仅可减少丙泊酚用药量,还可降低术后 POCD 的发生率,其机制可能与减轻机体炎症反应有关。

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·消 息·

《中华老年多器官疾病杂志》论文优先发表快速通道

为加快重大医学研究成果的交流推广，促进医学事业的发展，我刊对符合下列条件的论文开设快速通道，优先发表：(1)国家、军队、省部级基金资助项目；(2)其他具有国内领先水平的创新性科研成果论文；(3)相关领域各类最新指南解读。凡要求以“快速通道”发表的论文，作者应提供关于论文科学性和创新性的说明。我刊对符合标准的稿件，即快速审核及刊用。

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