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右美托咪定复合地佐辛静脉镇痛对老年腹腔镜胆囊切除术后患者 认知功能、氧化应激及炎症因子的影响*

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摘要 目的:探讨右美托咪定复合地佐辛静脉镇痛对老年腹腔镜胆囊切除术后患者认知功能、氧化应激及炎症因子的影响。**方法:**前瞻性选择 2017 年 4 月至 2019 年 12 月于我院拟行腹腔镜胆囊切除术的老年患者 103 例,采用随机数字表法将患者分为 A、B 两组。A 组 51 例,给予舒芬太尼镇痛,B 组 52 例,给予右美托咪定复合地佐辛静脉镇痛。对比两组不良反应、镇静、镇痛效果、认知功能、氧化应激及炎症因子。**结果:**B 组术后 12 h、24 h、48 h 视觉模拟评分法(VAS)评分低于 A 组($P<0.05$),B 组术后 12 h、24 h、48 h Ramsay 镇静评分高于 A 组($P<0.05$)。B 组术后 1 d、术后 3 d、术后 5 d 简易智能量表(MMSE)评分均高于 A 组($P<0.05$),B 组认知功能障碍(POCD)发生率低于 A 组($P<0.05$)。B 组术后 3 d、术后 5 d 丙二醛(MDA)低于 A 组,总抗氧化能力(T-AOC)、超氧化物歧化酶(SOD)高于 A 组($P<0.05$)。B 组术后 3 d、术后 5 d 白介素-6(IL-6)、超敏 C 反应蛋白(hs-CRP)、肿瘤坏死因子- α (TNF- α)低于 A 组($P<0.05$)。对比两组不良反应无差异($P>0.05$)。**结论:**与舒芬太尼相比,在地佐辛静脉镇痛基础上,加以右美托咪定,可在腹腔镜胆囊切除术后老年患者中取得较好镇痛镇静效果,可减轻其认知功能损害、氧化应激及炎症反应,且安全可靠。

关键词:右美托咪定;地佐辛;老年;腹腔镜胆囊切除术;认知功能;氧化应激;炎症因子

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Effects of Dexmedetomidine Combined with Dezocine on Cognitive Function, Oxidative Stress and Inflammatory Factors in Elderly Patients after Laparoscopic Cholecystectomy*

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ABSTRACT Objective: To investigate the effects of dexmedetomidine combined with dezocine on cognitive function, oxidative stress and inflammatory factors in elderly patients after laparoscopic cholecystectomy. **Methods:** 103 elderly patients who were planned to undergo laparoscopic cholecystectomy and admitted in our hospital from April 2017 to December 2019 were prospectively selected, patients were divided into group A, B by random number table method. 51 cases in group A, given sufentanil for analgesia, 52 cases in group B, given dexmedetomidine combined with dezocine intravenous analgesia. The adverse reactions, sedation, analgesic effect, cognitive function, oxidative stress and inflammatory factors were compared between the two groups. **Results:** The visual analogue scale (VAS) scores of group B were lower than those of group A at 12 h, 24 h, 48 h after operation ($P<0.05$), Ramsay sedation scores of group B were higher than those of group A at 12 h, 24 h and 48 h after operation ($P<0.05$). The scores of mini-mental state examination (MMSE) at 1 d after operation, 3 d after operation, 5 d after operation in group B were higher than those of group A ($P<0.05$), the incidence of postoperative cognitive dysfunction (POCD) in group B was lower than that of group A ($P<0.05$). Malondialdehyde (MDA) at 3 d after operation, 5 d after operation in group B were lower than those of group A, the total antioxidant capacity (T-AOC), superoxide dismutase (SOD) in group B were higher than those of group A ($P<0.05$). The levels of interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs CRP), tumor necrosis factor- α (TNF- α) at 3d after operation, 5 d after operation in group B were lower than those of group A ($P<0.05$). There was no difference in adverse reactions between the two groups ($P>0.05$). **Conclusion:** Compared with sufentanil, on the basis of dezocine intravenous analgesia, combined with dexmedetomidine, can obtain better analgesic and sedative effect in elderly patients with laparoscopic cholecystectomy, which can reduce cognitive impairment, oxidative stress and inflammatory reaction, and is safe and reliable.

Key words: Dexmedetomidine; Dezocine; Elderly; Laparoscopic cholecystectomy; Cognitive function; Oxidative stress; Inflammatory factors

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前言

胆囊切除术是一种常见术式,在胆外科应用广泛,可用于胆囊结石、胆囊炎等病的治疗^[1-3]。随着术式的发展,腹腔镜胆囊切除术受到广大医者及患者的青睐,此术式可减小创伤、减少出血、促进恢复,已经逐渐取代开腹胆囊切除,成为标准术式^[4]。尽管腹腔镜胆囊切除术优势显著,但仍属于有创操作,多项临床研究发现部分行腹腔镜胆囊切除术的患者围术期常发生疼痛,引起机体强烈的应激反应,降低手术治疗效果^[5]。尤其是老年腹腔镜胆囊切除术患者,因其自身身体机能减退,术后机体功能恢复延迟,易出现焦虑、神经错乱、人格改变和记忆受损等认知损害^[6]。此时,在围术期施以高效的麻醉方案,有利于促进患者预后的改善,在提升临床效果方面发挥着重要的作用^[7]。舒芬太尼是目前临床常用的麻醉药物,其镇痛效果好,药力持续时间长^[8]。地佐辛是一类较新的阿片类镇痛药,镇痛效果好,但单用药不良反应发生率较高^[9]。右美托咪定具有良好的镇静催眠、镇痛、抑制交感活性的作用^[10]。本研究设计了随机对照试验,探讨右美托咪定复合地佐辛静脉镇痛对老年腹腔镜胆囊切除术后患者认知功能、氧化应激及炎症因子的影响,旨在为临床中该术式麻醉方案的选取提供理论依据,现报道如下。

1 资料与方法

1.1 一般资料

前瞻性选择 2017 年 4 月至 2019 年 12 月于我院拟行腹腔镜胆囊切除术的老年患者 103 例,纳入标准:(1)年龄 ≥ 60 岁;(2)均符合手术指征者;(3)患有急慢性胆囊炎、胆囊结石、胆囊息肉等疾病者;(4)美国医师麻醉协会(ASA)分级 I~III 级者;(5)临床资料完整者。排除标准:(1)对本研究所用麻醉药物过敏者;(2)合并有癌症,心、肝、肾功能障碍等并发症患者;(3)已行腹腔镜手术者;(4)长期服用镇静和镇痛药物者;(5)存在精神病史者。采用随机数字表法将患者分为 A、B 两组,A 组 51 例,采用舒芬太尼镇痛,男 28 例,女 23 例,年龄 60~81 岁,平均(69.84 $\pm$ 2.67)岁;体质指数(BMI)20~27 kg/m²,平均(23.27 $\pm$ 0.88)kg/m²;ASA 分级^[11]:I 级 30 例,II 级 10 例,III 级 11 例;基础疾病:高血压 8 例,糖尿病 10 例。B 组 52 例,采用右美托咪定复合地佐辛静脉镇痛,男 29 例,女 23 例,年龄 62~79 岁,平均(69.15 $\pm$ 3.37)岁;BMI 21~26 kg/m²,平均(23.45 $\pm$ 0.93)kg/m²;ASA 分级:I 级 28 例,II 级 12 例,III 级 12 例;基础疾病:高血压 10 例,糖尿病 12 例。对比两组一般资料无差异($P>0.05$)。本研究获得我院医学伦理委员会批准,诊疗过程严格遵循伦理学原则,保障患者隐私和安全。

1.2 麻醉方法

两组术前常规禁饮禁食。入室后建立中心静脉通道,连接多功能心电监护仪,对两组患者心率(HR)、平均动脉压(MAP)等进行监测。麻醉诱导:依次静脉注射瑞芬太尼[江苏恩华药业股份有限公司,国药准字 H20143315,规格:2 mg(以瑞芬太尼计)]5 μ g/kg、罗库溴铵(N.V.Organon,批号 H20140847,规格:5 mL:50 mg)0.9 mg/kg 和异丙酚(Astra Seneca UK Limited,批号 20160646,规格:20 mL:200 mg)2 mg/kg,术中采用异丙酚 6~8 mg/(kg·h)、瑞芬太尼 5~7 mg/(kg·h)保持麻醉状态,同时

间断注射罗库溴铵保持肌松,手术完成前静脉注射地佐辛(扬子江药业集团有限公司,国药准字 H20080329,规格:1 mL:5 mg)5.0 mg、托烷司琼[太极集团四川太极制药有限公司,国药准字 H20090020,规格:2 mL:2 mg(以 C₁₇H₂₀N₂O₂ 计)]5.0 mg,完成缝皮后停止静脉麻醉。手术完成后,给予患者自控静脉镇痛(PCIA),A 组行以舒芬太尼(宜昌人福药业有限责任公司,国药准字 H20054172,规格:按 C₂₂H₃₀N₂O₂S 计 2 mL:100 μ g)1.5 μ g/kg 镇痛,并配制 100 mL 持续静脉泵注,设定持续与冲击剂量为 2 mL/h,时间为 15 min。B 组给予地佐辛 0.4 g/kg、右美托咪定[辰欣药业股份有限公司,国药准字 H20163388,规格:1 mL:0.1 mg(按右美托咪定计)]200 mg,并配制 100 mL 持续静脉泵注,设定持续与冲击剂量为 2 mL/h,时间为 15 min。

1.3 观察指标

统计两组术后 2 h、12 h、24 h、48 h 的视觉模拟评分法^[12](VAS)、Ramsay 镇静评分^[13]。其中 VAS 根据患者主观意见判定,视疼痛情况由无~重评分 0~10 分。Ramsay 镇静评分的分值范围为 1~6 分,其中烦躁不安为 1 分、安静合作为 2 分、嗜睡为 3 分、浅睡眠为 4 分、入睡为 5 分、深睡为 6 分。(1)于术前 1 d、术后 1 d、术后 3 d 和术后 5 d 使用简易智能量表^[14](MMSE)来评估患者的认知功能。MMSE 包括语言能力、定向力、注意力和计算力、回忆能力、记忆力,共 30 分,分数越高认知功能越好。认知功能障碍(POCD)诊断标准^[15]:MMSE 评分较术前评分下降 2 分或 2 分以上即可判定发生了 POCD。(2)采集患者术前、术后 3 d、术后 5 d 非输液侧肢体静脉血标本 6 mL,经 4℃、3300 r/min 离心 17 min(离心半径 10 cm),分离上清液。酶联免疫吸附法检测白介素-6(IL-6)、超敏 C 反应蛋白(hs-CRP)、肿瘤坏死因子- α (TNF- α),仪器为意大利 BIOBASE2000 全自动酶免分析仪,试剂盒为仪器配套试剂盒。丙二醛(MDA)水平采用硫代巴比妥酸法测定,总抗氧化能力(T-AOC)由 FRAP 法测定,采用黄嘌呤氧化酶法检测超氧化物歧化酶(SOD)水平,试剂盒由美国贝克曼公司生产。严格按说明书执行操作。(3)统计两组不良反应。

1.4 统计学分析

使用 SPSS25.0 进行研究资料分析。观测资料中的计量数据,均通过正态性检验,以 MEAN $\pm$ SD 描述。两组间的比较为成组 t 检验或校正 t 检验(统计量为 t)。重复观测资料则行重复测量方差分析(球检验校正为 HF 法,统计量为 F)+两两组间比较 LSD-t 检验(统计量为 LSD-t)+两两组内(时间维度)比较差值 t 检验(统计量为 t)。计数资料以例数及率描述。组间比较为卡方检验或校正卡方检验(统计量为 χ^2)。统计推断的检验水准 $\alpha=0.05$ (双侧检验), $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组 VAS、Ramsay 镇静评分对比

整体比较显示,各指标组间差异、组内(时间维度)差异及交互作用均有显著性意义($P<0.05$)。两两精细比较并结合主要数据分析显示,两组术后 12 h、24 h、48 h VAS 评分呈升高后降低趋势,B 组术后 12 h、24 h、48 h VAS 评分低于 A 组($P<0.05$),A 组术后 12 h、24 h、48 h Ramsay 镇静评分呈依次下降趋势,B 组术后 2 h、术后 12 h、24 h、48 h Ramsay 镇静评分组内对

比差异无统计学意义($P>0.05$),B 组术后 12 h、24 h、48 h Ramsay 镇静评分高于 A 组($P<0.05$),详见表 1。

表 1 两组 VAS、Ramsay 镇静评分对比($\bar{x}\pm s$,分)

Table 1 Comparison of VAS, Ramsay sedation score between the two groups($\bar{x}\pm s$, score)

Groups	Time	VAS	Ramsay sedation score
Group A(n=51)	2 h after operation	1.38 $\pm$ 0.25	2.46 $\pm$ 0.22
	12 h after operation	2.29 $\pm$ 0.31 ^t	2.23 $\pm$ 0.17 ^t
	24 h after operation	3.33 $\pm$ 0.34 ^t	2.01 $\pm$ 0.12 ^t
	48 h after operation	2.71 $\pm$ 0.29 ^t	1.83 $\pm$ 0.18 ^t
Group B(n=52)	2 h after operation	1.35 $\pm$ 0.26	2.52 $\pm$ 0.29
	12 h after operation	1.87 $\pm$ 0.31 ^{at}	2.48 $\pm$ 0.24 ^a
	24 h after operation	2.80 $\pm$ 0.32 ^{at}	2.46 $\pm$ 0.29 ^a
	48 h after operation	2.24 $\pm$ 0.28 ^{at}	2.44 $\pm$ 0.27 ^a
The overall analysis	HF coefficient	0.9902	0.8897
Comparison between groups	F, P	123.962, 0.000	252.822, 0.000
Comparison in the group	F, P	628.769, 0.000	43.914, 0.000
Interaction	F, P	15.817, 0.000	26.533, 0.000

Note: Two-factor repeated measurement ANOVA was used for the overall analysis, and HF coefficient method was used to correct the sphericity of data. Fine comparison between groups was performed by LSD-t test, and significant marker "a" was the comparison between the two groups at the same time ($P<0.05$). Fine comparison within the group (time dimension) was the difference t-test, and significance marker "t" was the comparison with the first time point within the group ($P<\alpha'$), α' was Bonferroni's corrected test level $=0.05/3=0.017$, "3" is the number of detailed comparisons in time dimension.

2.2 两组认知功能

整体比较显示,组间差异、组内(时间维度)差异及交互作用均有显著性意义($P<0.05$)。两两精细比较并结合主要数据

分析显示,两组术后 1 d、3 d、5 d MMSE 评分呈先降低后升高趋势,B 组术后 1 d、术后 3 d、术后 5 d MMSE 评分均高于 A 组($P<0.05$)。此外,B 组 POCD 发生率较 A 组更低($P<0.05$),见表 2。

表 2 两组认知功能对比

Table 2 Comparison of cognitive function between the two groups

Groups	Time	MMSE scores(score)	Incidence rate of POCD[n(%)]
Group A(n=51)	1 d before operation	29.22 $\pm$ 0.26	9(17.65)
	1 d after operation	25.36 $\pm$ 0.96 ^t	
	3 d after operation	27.04 $\pm$ 0.67 ^t	
	5 d after operation	28.09 $\pm$ 0.57 ^t	
Group B(n=52)	1 d before operation	29.21 $\pm$ 0.35	2(3.85)
	1 d after operation	27.12 $\pm$ 0.73 ^{at}	
	3 d after operation	28.32 $\pm$ 0.59 ^{at}	
	5 d after operation	29.01 $\pm$ 0.67 ^{at}	
The overall analysis	HF coefficient	0.8561	-
Comparison between groups	F(x^2), P	267.927, 0.000	(4.139), 0.042
Comparison in the group	F, P	411.919, 0.000	-
Interaction	F, P	35.148, 0.000	-

Note: Same as table 1.

2.3 两组氧化应激指标

整体比较显示,组间差异、组内(时间维度)差异及交互作用均有显著性意义($P<0.05$)。两两精细比较并结合主要数据分析显示,两组术后 3 d、术后 5 d MDA 呈降低趋势,T-AOC、

SOD 呈升高趋势,B 组术后 3 d、术后 5 d MDA 低于 A 组,T-AOC、SOD 高于 A 组($P<0.05$),详见表 3。

2.4 两组炎症因子指标对比

整体比较显示,组间差异、组内(时间维度)差异及交互作用

用均有显著性意义($P<0.05$)。两两精细比较并结合主要数据 B 组术后 3 d、5 d IL-6、hs-CRP、TNF- α 较 A 组更低($P<0.05$)，分析显示，两组术后 3 d、5 d IL-6、hs-CRP、TNF- α 呈降低趋势，见表 4。

表 3 两组氧化应激指标对比($\bar{x}\pm s$)

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

Groups	Time	MDA(mmole/L)	T-AOC(U/mL)	SOD(U/mL)
Group A(n=51)	Before operation	2.42 $\pm$ 0.23	19.17 $\pm$ 2.60	82.29 $\pm$ 5.25
	3 d after operation	14.60 $\pm$ 0.48 ^t	6.97 $\pm$ 1.54 ^t	34.19 $\pm$ 6.70 ^t
	5 d after operation	8.59 $\pm$ 0.36 ^t	10.04 $\pm$ 1.33 ^t	51.14 $\pm$ 7.19 ^t
Group B(n=52)	Before operation	2.47 $\pm$ 0.25	19.20 $\pm$ 1.64	82.43 $\pm$ 7.12
	3 d after operation	10.70 $\pm$ 0.34 ^{at}	10.20 $\pm$ 1.28 ^{at}	48.92 $\pm$ 7.02 ^{at}
	5 d after operation	5.17 $\pm$ 0.32 ^{at}	15.16 $\pm$ 1.96 ^{at}	63.41 $\pm$ 5.98 ^{at}
The overall analysis	HF coefficient	0.5515	0.8255	0.9643
Comparison between groups	F, P	4,474.184, 0.000	212.491, 0.000	136.290, 0.000
Comparison in the group	F, P	21,767.623, 0.000	867.399, 0.000	1,028.900, 0.000
Interaction	F, P	968.575, 0.000	50.046, 0.000	37.024, 0.000

Note: Same as table 1, α' was Bonferroni's corrected test level =0.05/2=0.025.

表 4 两组炎症因子指标对比($\bar{x}\pm s$)

Table 4 Comparison of inflammatory factors between the two groups($\bar{x}\pm s$)

Groups	Time	IL-6(pg/mL)	hs-CRP(mg/L)	TNF- α (pg/mL)
Group A(n=51)	Before operation	16.23 $\pm$ 2.73	19.75 $\pm$ 1.46	15.65 $\pm$ 2.96
	3 d after operation	127.73 $\pm$ 19.85 ^t	96.41 $\pm$ 12.52 ^t	93.90 $\pm$ 15.22 ^t
	5 d after operation	88.28 $\pm$ 16.46 ^t	71.78 $\pm$ 8.47 ^t	66.28 $\pm$ 10.74 ^t
Group B(n=52)	Before operation	16.17 $\pm$ 2.78	20.00 $\pm$ 2.78	15.84 $\pm$ 2.20
	3 d after operation	83.73 $\pm$ 21.36 ^{at}	71.15 $\pm$ 9.61 ^{at}	68.51 $\pm$ 13.55 ^{at}
	5 d after operation	55.19 $\pm$ 14.25 ^{at}	44.35 $\pm$ 7.00 ^{at}	43.23 $\pm$ 9.08 ^{at}
The overall analysis	HF coefficient	0.8890	0.9590	0.9373
Comparison between groups	F, P	184.755, 0.000	386.681, 0.000	184.143, 0.000
Comparison in the group	F, P	1,052.679, 0.000	1,629.830, 0.000	1,074.656, 0.000
Interaction	F, P	67.430, 0.000	93.399, 0.000	49.530, 0.000

Note: Same as table 1, α' was Bonferroni's corrected test level =0.05/2=0.025.

2.5 两组不良反应对比

A 组治疗期间出现恶心呕吐 2 例、寒战 1 例、头晕 1 例，不良反应发生率为 7.84%(4/51)；B 组恶心呕吐 2 例、寒战 2 例，不良反应发生率为 9.62%(4/52)；对比两组不良反应无差异($\chi^2=0.115$, $P=0.734$)。

3 讨论

腹腔镜胆囊切除术中需建立二氧化碳气腹，同时手术牵拉内脏组织等操作会对机体产生刺激，进而引起炎症反应，造成术后疼痛、引发人体氧化应激及内脏功能损伤、POCD 等并发症^[16-18]。其中 POCD 多发于老年群体，还可以发展为永久性的认知障碍。现有的研究认为，POCD 的发生与术中事件、术后疼痛、患者年龄、机体受损程度等息息相关^[19]。可见如果能在术后给患者提供良好的镇痛镇静，减轻机体炎性及氧化应激反应，

对于改善老年腹腔镜胆囊切除术患者预后具有积极的促进意义。PCIA 是目前临床常用的术后镇痛方式，但在具体的镇痛剂配选上，不同的麻醉师可能会有不同的用药方案，其中右美托咪定、舒芬太尼、地佐辛等较为常见^[20]。舒芬太尼为芬太尼家族成员之一，是一种作用于 μ 阿片受体的激动药物，既往研究显示其镇痛持续时间是芬太尼的 2 倍，且镇痛效果是芬太尼的 5 倍以上，镇痛效果较好^[21]。而张之翠等^[22]学者研究表明，地佐辛用于腹腔镜胆囊手术后镇痛，可获得与舒芬太尼相当的镇痛效果，且呼吸抑制和镇静过度发生率低于舒芬太尼。作为一种阿片类镇痛药，地佐辛同时也是 μ 受体拮抗剂、 κ 受体激动剂，但部分临床实践显示单用此药存在成瘾风险^[23,24]。右美托咪定是新型 α_2 肾上腺素能受体激动剂，呼吸抑制程度轻^[25]。商燕等^[26]人的研究中，右美托咪定联合地佐辛用于开胸手术术后镇痛中，镇痛效果确切，可改善患者认知水平，有助于降低炎症因子

水平。故笔者尝试将右美托咪定复合地佐辛应用于老年腹腔镜胆囊切除术后患者的镇痛中,以期获得相对理想的麻醉效果。

本研究显示,B组术后VAS评分、Ramsay镇静评分优于A组,且对比两组不良反应无差异。提示在地佐辛基础上,联合右美托咪定镇静、镇痛效果、安全性均较好。地佐辛通过产生呼吸抑制、脊髓镇痛及轻度的镇静效果对患者进行术后镇痛。右美托咪定可与突触前 α_2 肾上腺素能受体发生作用,从而使得去甲肾上腺素的释放减少,进而发挥阻断疼痛信号传递的功效;除以上效用外,右美托咪定还能发挥遏制交感神经活性的作用,从而维持机体血流平稳,发挥镇静及抗焦虑作用^[27]。

手术创伤、麻醉、术后疼痛等刺激导致大量儿茶酚胺、细胞因子、肾上腺皮质激素释放,加上老年患者自身免疫力低下,常合并多种基础性疾病,在上述刺激下更容易出现强烈的应激反应,表现为全身炎症反应及氧化应激^[28]。IL-6是早期促炎细胞因子之一^[29],hs-CRP、TNF- α 是早期炎症反应敏感指标,监测IL-6、hs-CRP、TNF- α 浓度可有效反映患者机体炎症反应程度。MDA、T-AOC、SOD均是反映氧化应激程度的常见指标,其中机体损伤程度越大,SOD消耗越严重^[30];MDA是脂质过氧化的最终产物,可间接反映组织中氧自由基含量^[31];T-AOC是机体抗氧化物质及对抗氧化损伤能力的总和^[32]。本研究结果发现,相对于舒芬太尼镇痛,右美托咪定复合地佐辛静脉镇痛可减轻机体氧化应激程度,降低机体炎症反应。这可能与右美托咪定可降低交感神经系统活性,抑制免疫细胞损伤应答反应有关。国外有报道显示右美托咪定可有效降低围术期炎症反应,发挥对脏器的保护作用^[33]。另一方面,POCD近年来逐渐引起了临床工作者的关注,关于POCD的具体发病原理,目前尚不清楚,但既往研究表明应激反应、全身炎症反应、过度磷酸化均在POCD的发展过程中参与重要作用^[34]。本次结果提示右美托咪定复合地佐辛静脉镇痛可发挥保护机体认知功能的作用,患者术后POCD的发生率明显降低。

综上所述,与舒芬太尼相比,在地佐辛静脉镇痛基础上,加以右美托咪定,可在老年腹腔镜胆囊切除术后患者中取得较好镇静、镇痛效用,可减轻其认知功能损害、氧化应激及炎症反应,且不增加不良反应发生率。

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