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右美托咪定对老年恶性肿瘤全麻手术患者术后细胞免疫功能、认知功能及炎症因子水平的影响*

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摘要 目的:探讨右美托咪定对老年恶性肿瘤全麻手术患者术后细胞免疫功能、认知功能及炎症因子水平的影响。**方法:**选取 2017 年 2 月~2019 年 6 月期间到我院择期行手术治疗的老年恶性肿瘤患者 119 例,根据随机数字表法将患者分为对照组($n=59$)和研究组($n=60$),研究组麻醉中输注右美托咪定,对照组麻醉中输注同容量等速率的生理盐水,比较两组患者围术期指标、细胞免疫功能、不良反应、炎症因子指标、简易智力状态量表(MMSE)评分。**结果:**两组患者术后第 3 d 的 $CD4^+/CD8^+$ 、 $CD3^+$ 、 $CD4^+$ 较术前下降, $CD8^+$ 较术前升高($P<0.05$);研究组术后第 3 d 的 $CD4^+/CD8^+$ 、 $CD3^+$ 、 $CD4^+$ 高于对照组, $CD8^+$ 则低于对照组($P<0.05$)。两组术后第 3 d 的血清高迁移率蛋白 1(HMGB1)、白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)水平均升高,但研究组低于对照组($P<0.05$)。两组手术时间、术中出血量、麻醉时间比较无差异($P>0.05$)。两组患者术前、术后第 1 d、术后第 3 d 的 MMSE 评分呈先下降后上升趋势($P<0.05$),且研究组术后第 1 d、第 3 d 的 MMSE 评分高于对照组($P<0.05$)。两组不良反应发生率比较无统计学差异($P>0.05$)。**结论:**老年恶性肿瘤全麻手术患者术中输注右美托咪定,可减轻细胞免疫抑制及炎症反应,对术后早期的认知功能下降有一定预防作用。

关键词:右美托咪定;老年;恶性肿瘤;全麻;细胞免疫;认知功能;炎症因子

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The Effect of Dexmedetomidine on the Cellular Immune Function, Cognitive Function and Inflammatory Factors in the Elderly Patients Undergoing General Anesthesia*

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ABSTRACT Objective: To investigate the effect of dexmedetomidine on the cellular immune function, cognitive function and inflammatory factors in the elderly patients undergoing general anesthesia. **Methods:** A total of 119 patients with malignant tumors in our hospital from February 2017 to June 2019 were selected for operation treatment. According to the method of random number table, the patients were divided into control group ($n=59$) and study group ($n=60$). In the study group, dexmedetomidine was infused during anesthesia, while in the control group, normal saline with the same volume and the same rate was infused during anesthesia. The perioperative indexes, cellular immune function and Mini-mental State Examination (MMSE) score and inflammatory factors of the two groups were compared, and adverse reactions of the two groups during the treatment were recorded. **Results:** The $CD4^+/CD8^+$, $CD3^+$, $CD4^+$ of the patients in the two groups on the 3d after operation were decreased, and the $CD8^+$ increased compared with the preoperative ($P<0.05$). The $CD4^+/CD8^+$, $CD3^+$, $CD4^+$ in the study group on the 3d after operation were higher than those in the control group, and $CD8^+$ was lower than that in the control group ($P<0.05$). The levels of high mobility group protein 1 (HMGB1), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) in the serum of the two groups on the 3d after operation were all increased, but those in the study group were lower than those in the control group ($P<0.05$). There were no significant differences in intraoperative hemorrhage volume, operation time and anesthesia time between the two groups ($P>0.05$). The MMSE score of the 1 d and 3 d after operation in the two groups decreased first and then increased ($P<0.05$). The MMSE score of the 1 d and 3 d after operation in the study group were higher than that in the control group ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** The infusion of dexmedetomidine during the operation of general anesthesia for the elderly cancer patients can reduce the cellular immunosuppression and inflammatory response, which has a certain preventive effect on the early postoperative cognitive decline.

Key words: Dexmedetomidine; Elderly; Malignant tumor; General anesthesia; Immune function; Cognitive function; Inflammatory

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前言

恶性肿瘤是影响老年人生命和健康最重要的因素之一,据统计,65岁以上人群最容易患恶性肿瘤,恶性肿瘤患者的发病率和死亡率最高^[1]。外科手术是治疗恶性肿瘤常见的方式,可有效阻止疾病进展。由于手术作为一种创伤性操作,可引起机体强烈的应激反应及免疫抑制,影响手术效果^[2,3]。全麻时的气管插管等侵入性操作可增加患者感染发生率,术中麻醉药物的应用不当还可引起误吸、苏醒期躁动等,甚至可并发术后认知功能障碍^[4,5]。因此,全麻术中合理的麻醉药物选择对于改善恶性肿瘤患者预后具有积极的临床意义。右美托咪定是 α_2 -肾上腺素受体激动剂,因其独特的镇痛、镇静作用而受到麻醉医师的广泛关注^[6,7]。本研究通过对我院进行治疗的部分恶性肿瘤老年患者给予右美托咪定麻醉,取得了较好的效果,现整理报道如下。

1 资料与方法

1.1 一般资料

选取2017年2月~2019年6月期间到我院择期行手术治疗的恶性肿瘤老年患者119例,本研究经我院伦理委员会批准同意。纳入标准:(1)所有患者均经病理实验确诊为恶性肿瘤;(2)均符合手术指征者;(3)对本研究使用药物无禁忌症者;(4)美国麻醉医师协会(American Society of Anesthesiologists, ASA)分级I~II级者;(5)患者及其家属对研究内容知情并已签署同意书;(6)年龄 ≥ 60 岁。排除标准:(1)合并精神疾患无法配合治疗者;(2)合并多种恶性肿瘤者;(3)入组前3个月内使用过免疫调节剂者;(4)术前接受过放化疗者。根据随机数字表法将患者分为对照组($n=59$)和研究组($n=60$),其中对照组男32例,女27例,年龄60~82岁,平均 (72.06 ± 3.91) 岁;ASA分级I级33例,II级26例;体质指数 $21.6 \sim 25.3 \text{ kg/m}^2$,平均 $(23.51 \pm 0.57) \text{ kg/m}^2$;肿瘤类型:胃癌22例,食管癌19例,肝癌10例,其他8例。研究组男35例,女25例,年龄62~79岁,平均 (71.54 ± 4.16) 岁;ASA分级I级31例,II级29例;体质指数 $21.9 \sim 24.8 \text{ kg/m}^2$,平均 $(23.82 \pm 0.66) \text{ kg/m}^2$;肿瘤类型:胃癌24例,食管癌17例,肝癌9例,其他10例。两组一般资料比较无差异($P>0.05$)。

1.2 麻醉方法

入院后患者均确诊为恶性肿瘤,择期给予手术治疗。两组患者术前常规禁饮、禁食,常规监测患者心率、平均动脉压等。两组患者均采用全麻,麻醉诱导:依次静脉滴注咪达唑仑(江苏恩华药业股份有限公司,规格:2 mL:10 mg,国药准字H10980025)0.05 mg/kg,丙泊酚(江苏恩华药业股份有限公司,规格:20 mL:0.2 g,国药准字H20123138)1.0 mg/kg,舒芬太尼(宜昌福人药业有限责任公司,规格:1 mL:50 μg (以舒芬太尼计),国药准字H20054171)0.4 $\mu\text{g/kg}$,注射用苯磺顺阿曲库铵(上药东英(江苏)药业有限公司,规格:5 mg,国药准字

H20060927)0.2 mg/kg,诱导成功后气管插管,麻醉维持:七氟烷0.8~1.0 MAC,手术结束前0.5 h停止吸入七氟烷,手术结束时停止泵注静脉麻醉药。研究组在气管插管后持续静脉输注右美托咪定(江苏恒瑞医药股份有限公司,国药准字H20090248,规格:2 mL:200 μg (按右美托咪定计))0.3 $\mu\text{g}/(\text{kg} \cdot \text{h})$,手术结束前30 min停止。对照组则在气管插管后输注同容量等速率的生理盐水。两组术后均常规给予抗炎、抗感染等对症治疗。

1.3 观察指标

于术前、术后第3 d抽取患者清晨空腹静脉血8 mL,经离心半径12 cm,4300 r/min离心11 min,取上清液分装两管保存于 -20°C 冰箱中待测。其中一管采用美国Beckman CX5全自动生化分析仪检测免疫功能指标 $\text{CD}3^+$ 、 $\text{CD}4^+$ 、 $\text{CD}8^+$,并计算 $\text{CD}4^+/\text{CD}8^+$ 。另一管根据试剂盒(购自武汉博士德生物科技有限公司)说明书进行操作,采用酶联免疫吸附法检测高迁移率族蛋白1(High mobility group protein 1, HMGB1)、白介素-6(Interleukin-6, IL-6)、肿瘤坏死因子- α (Tumor necrosis factor- α , TNF- α)水平。统计两组患者围术期不良反应发生情况。记录两组患者术中出血量、手术时间、麻醉时间。于术前、术后第1 d、术后第3 d采用简易智力状态量表(Mini-mental State Examination, MMSE)^[8]评价两组患者的认知功能,其中MMSE满分为30分,包括回忆能力、注意力、定向力、语言能力、计算力、记忆力6个方面,评分越高说明认知功能越佳。

1.4 统计学方法

研究数据录入SPSS23.0软件处理。计数资料以率(%)表示,比较采用卡方检验。计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,比较采用t检验。检验水准 $\alpha=0.05$ 。

2 结果

2.1 细胞免疫功能指标比较

两组术前 $\text{CD}4^+/\text{CD}8^+$ 、 $\text{CD}3^+$ 、 $\text{CD}8^+$ 、 $\text{CD}4^+$ 比较无差异($P>0.05$);两组术后第3 d $\text{CD}4^+/\text{CD}8^+$ 、 $\text{CD}3^+$ 、 $\text{CD}4^+$ 较术前下降, $\text{CD}8^+$ 较术前升高($P<0.05$);研究组术后第3 d $\text{CD}4^+/\text{CD}8^+$ 、 $\text{CD}3^+$ 、 $\text{CD}4^+$ 高于对照组, $\text{CD}8^+$ 则低于对照组($P<0.05$);详见表1。

2.2 炎症因子指标比较

两组术前血清HMGB1、IL-6、TNF- α 水平比较无差异($P>0.05$);两组术后第3 d血清HMGB1、IL-6、TNF- α 水平均升高,但研究组低于对照组($P<0.05$);详见表2。

2.3 围术期指标比较

两组患者术中出血量、手术时间、麻醉时间比较无统计学差异($P>0.05$);详见表3。

2.4 认知功能评分比较

两组患者术前MMSE评分比较无统计学差异($P>0.05$);两组患者术后第1 d、术后第3 d的MMSE评分呈先下降后升高趋势($P<0.05$);研究组术后第1 d、术后第3 d的MMSE评分高于对照组($P<0.05$);详见表4。

表 1 细胞免疫功能指标比较($\bar{x} \pm s$)Table 1 Comparison of cellular immune function indexes($\bar{x} \pm s$)

Groups	CD3 ⁺ (%)		CD4 ⁺ (%)		CD8 ⁺ (%)		CD4 ⁺ /CD8 ⁺	
	Preoperative	3 d after operation	Preoperative	3 d after operation	Preoperative	3 d after operation	Preoperative	3 d after operation
Control group (n=59)	57.93± 8.23	45.59± 7.06*	37.78± 4.12	24.98± 5.82*	28.38± 3.43	35.43± 4.12*	1.33± 0.29	0.71± 0.09*
Study group (n=60)	58.83± 7.09	52.18± 7.23*	36.73± 4.23	30.82± 4.87*	27.89± 3.69	31.08± 4.58*	1.32± 0.25	0.99± 0.14*
t	0.639	5.030	1.371	5.940	0.751	5.444	0.202	12.954
P	0.524	0.000	0.137	0.000	0.454	0.000	0.841	0.000

Note: Compared with preoperative, * $P<0.05$.表 2 炎症因子指标比较($\bar{x} \pm s$)Table 2 Comparison of inflammatory factors indexes($\bar{x} \pm s$)

Groups	HMGBI(ng/mL)		IL-6(pg/mL)		TNF- α (pg/mL)	
	Preoperative	3 d after operation	Preoperative	3 d after operation	Preoperative	3 d after operation
Control group (n=59)	28.12± 4.84	45.28± 6.33*	11.32± 2.92	33.38± 6.09*	42.83± 5.73	63.74± 6.28*
Study group(n=60)	27.34± 3.24	36.29± 5.89*	11.94± 2.22	20.29± 5.02*	41.37± 5.34	54.12± 5.98*
t	1.035	8.022	1.305	12.804	1.438	8.559
P	0.303	0.000	0.194	0.000	0.153	0.000

Note: Compared with preoperative, * $P<0.05$.表 3 围术期指标比较($\bar{x} \pm s$)Table 3 Comparison of perioperative indexes($\bar{x} \pm s$)

Groups	Intraoperative hemorrhage volume(mL)	Operative time(min)	Anesthesia time(min)
Control group(n=59)	212.43± 17.12	119.01± 9.83	147.32± 8.12
Study group(n=60)	208.98± 19.27	121.59± 10.02	146.12± 8.44
t	1.032	1.418	0.801
P	0.304	0.159	0.425

表 4 认知功能评分比较($\bar{x} \pm s$,分)Table 4 Comparison of cognitive function scores($\bar{x} \pm s$, score)

Groups	MMSE scores		
	Preoperative	1 d after operation	3 d after operation
Control group(n=59)	28.43± 0.32	24.01± 0.83*	26.32± 0.42**
Study group(n=60)	28.38± 0.47	26.59± 0.52*	28.19± 0.44**
t	0.677	20.356	23.708
P	0.500	0.000	0.000

Note: Compared with preoperative, * $P<0.05$; compared with 1 d after operation, ** $P<0.05$.

2.5 不良反应情况比较

对照组术中出现 2 例恶心、4 例呕吐、2 例低血压、4 例寒战,不良反应发生率为 20.34%(12/59),研究组出现 3 例恶心、2 例呕吐、4 例低血压、5 例寒战,不良反应发生率为 23.33%(14/60),两组不良反应发生率比较无统计学差异($\chi^2=0.156$, $P=0.693$)。

3 讨论

恶性肿瘤是临床常见的疾病,其治疗方式包括保守放化疗治疗、外科手术治疗,其中以外科手术治疗最为简便有效^[9,10]。随着医学检测技术的发展,早期恶性肿瘤的检出率不断提升,接受手术治疗的恶性肿瘤患者增多。肿瘤患者自身亦可通过免

疫调节来抑制或杀灭循环中的肿瘤细胞,但围术期的各种创伤、麻醉药物的使用、术中的疼痛等均可导致机体不同程度的应激反应,破坏机体正常循环,致使炎症因子的大量分泌、免疫功能受到抑制,降低了机体对残存的肿瘤细胞的控制能力^[11-13]。老年群体自身机能不足,且原发疾病较多,身体恢复能力较差,术中强烈的应激反应还可导致患者术后不同程度的认知功能障碍^[14,15]。全麻虽然可以为老年恶性肿瘤患者实施手术提供良好的手术条件,但全麻手术中使用的麻醉药物引发的认知功能障碍风险及不良反应问题也得到重点关注,右美托咪定作为一种麻醉辅助药广泛的应用于各类手术中,尤其在全麻中其应用价值进一步凸显^[16,17]。

正常机体的免疫功能与肿瘤的发生发展密切相关,CD4⁺经抗原呈递细胞致敏后可产生多种细胞因子,可直接杀伤肿瘤细胞;CD3⁺代表T淋巴细胞免疫的总体水平;CD4⁺/CD8⁺之间的平衡被打破也将影响机体的抗肿瘤免疫^[18-20]。本研究结果显示,两组患者术后均表现出不同程度的免疫抑制,但研究组的免疫抑制程度更轻,此外,两组患者围术期指标、不良反应发生率比较无差异,可见右美托咪定可有效减轻老年恶性肿瘤全麻手术患者免疫功能抑制,且对围术期指标的影响轻微,不会增加不良反应,这是因为右美托咪定可减少儿茶酚胺的释放,抑制神经交感活动,继而发挥良好的稳定血流动力学作用,减轻手术对机体造成的刺激,从而不增加不良反应,并减轻手术对细胞免疫功能的抑制^[21,22]。HMGB1是一种晚期炎症因子,可诱导炎症因子大量释放^[23,24]。本次研究结果中,右美托咪定应用于老年恶性肿瘤全麻手术患者,可明显降低炎症因子如血清IL-6、HMGB1、TNF- α 的分泌,其作用机制可能在于右美托咪定激活 $\alpha 2$ 肾上腺素受体,通过调控细胞外信号调节蛋白激酶,进而激活单核细胞烟碱型乙酰胆碱受体,从而抑制单核细胞Toll样受体的表达,降低其介导的下游炎症因子的释放^[25,26]。既往不少基础试验及临床研究均证实右美托咪定对炎症因子如IL-6、TNF- α 具有一定的抑制作用^[27]。本次研究结果还显示,研究组术后第1d、术后第3d的MMSE评分高于对照组,可见右美托咪定对患者术后早期的认知功能下降有一定的预防作用,其预防作用可能与右美托咪定可减少兴奋性的神经递质释放、减少脑组织释放的肾上腺素、抑制钙离子内流有关,可发挥较好的脑保护效果,同时其极强的镇静、镇痛作用,也可降低疼痛所引发的认知功能障碍的发生风险^[28-30]。

综上所述,老年恶性肿瘤全麻手术患者术中使用右美托咪定可减轻细胞免疫抑制,改善炎症应激,降低手术对患者术后认知功能的影响。

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