·老年患者围术期管理专栏·

七氟醚吸入麻醉和丙泊酚静脉麻醉对老年肺癌根治术患者血清 VEGF、VCAM-1、MMP-2 和 MMP-9 表达的影响

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【摘 要】 目的 通过比较七氟醚吸入麻醉和丙泊酚静脉麻醉对老年肺癌根治术患者血清血管内皮生长因子(VEGF)、血管细胞黏附分子-1(VCAM-1)、基质金属蛋白酶-2(MMP-2)和 MMP-9 表达的影响,进一步为临床麻醉选择提供参考。**方法** 择期行肺癌根治术老年患者60例,年龄60~75岁,ASAⅠ~Ⅱ级,采用随机数字表法将60例患者分为七氟醚组(S组)和丙泊酚组(P组),每组30例。S组患者气管插管后持续吸入1.7%~3.4%的七氟醚至术毕,术中维持呼气末七氟醚浓度为1~2 MAC,P组患者气管插管后持续静脉输注丙泊酚至术毕,术中丙泊酚效应室浓度维持在1.5~3.0 μg/ml。分别于麻醉诱导前即刻(T0)、手术开始后1h(T1)、手术开始后2 h(T2)、手术结束后1 h(T3)、手术结束后2 h(T4)抽取静脉血2 ml,采用酶联免疫吸附法检测两组患者血清 VEGF、VCAM-1、MMP-2 和 MMP-9 表达。**结果** 与T0时比较,S组T1~T4时血清 VEGF 及 VCAM-1 表达降低($P<0.05$),T2~T4时 MMP-2 和 MMP-9 表达降低($P<0.05$);P组T1~T4时血清 VEGF、VCAM-1、MMP-2 和 MMP-9 表达无明显差异($P>0.05$)。与P组比较,S组T2~T4时血清 VEGF、VCAM-1、MMP-2 和 MMP-9 表达降低($P<0.05$)。**结论** 与丙泊酚静脉麻醉相比七氟醚吸入麻醉能抑制老年肺癌根治术患者血清 VEGF、VCAM-1、MMP-2 和 MMP-9 的表达。

【关键词】 七氟醚;丙泊酚;肺癌;血管内皮生长因子;血管细胞黏附分子-1;基质金属蛋白酶-2;基质金属蛋白酶-9
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Effects of sevoflurane inhalation and propofol intravenous anesthesia on plasma levels of VEGF, VCAM-1, MMP-2 and MMP-9 in the elderly undergoing radical surgery for lung cancer

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【Abstract】 Objective To compare the effects of sevoflurane inhalational anesthesia and propofol intravenous anesthesia on the plasma levels of vascular endothelial growth factor (VEGF), vascular cell adhesion molecule-1 (VCAM-1), matrix metalloproteinase-2 (MMP-2) and MMP-9 in the elderly patients undergoing radical surgery for lung cancer, and provide further reference for the options of clinical anesthesia. **Methods** Sixty ASA Ⅰ or Ⅱ lung cancer patients at the grade of American Society of Anesthesiologists (ASA) Ⅰ or Ⅱ and aged 60 to 75 years undergoing radical surgery for lung cancer in our hospital were recruited in this study, and randomly divided into 2 groups ($n=30$): sevoflurane group (group S) and propofol group (group P). After tracheal intubation, 1.7% -3.4% sevoflurane were given to the group S, and maintained its end-tidal of 1-2 MAC until the end of surgery, while, 1.5-3.0 μg/ml target effect-site concentration of propofol was given through controlled infusion in group P until the end. Venous blood samples of 2 ml were harvested at just before induction of anesthesia (T0), 1 h after surgery beginning (T1), 2 h after surgery beginning (T2), 1 h after the end of surgery (T3), and 2 h after the end of surgery (T4) for the levels of VEGF, VCAM-1, MMP-2 and MMP-9 by enzyme linked immunosorbent assay (ELISA). **Results** Compared with T0, the plasma levels of VEGF and VCAM-1 were significantly decreased in group S at T1-T4 ($P<0.05$), and those of MMP-2 and MMP-9 were also reduced at T2-T4 ($P<0.05$). But no such differences were found in group P at T1-T4 ($P>0.05$). The levels of above indicators were obviously lower in group S than in group P at the period ($P<0.05$). **Conclusion** Compared with propofol intravenous anesthesia, sevoflurane inhalation can inhibit the expression of VEGF, VCAM-1, MMP-2 and MMP-9 in the elderly patients undergoing radical surgery for lung cancer.

【Key words】 sevoflurane; propofol; lung cancer; vascular endothelial growth factor; vascular cell adhesion molecule-1; matrix metalloproteinase-2; matrix metalloproteinase-9

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肺癌是世界各国常见的呼吸道恶性肿瘤。手术切除是治疗肺癌的方法之一,但术后肿瘤的复发或转移仍然是肺癌患者死亡的主要原因[1]。不同的麻醉药物和麻醉方法对肿瘤细胞生长和侵袭能力的影响存在差异,并和肿瘤患者术后的转归密切相关[2,3]。七氟醚是目前临床常用的吸入麻醉药,广泛用于肺癌手术的麻醉。体外研究表明,七氟醚具有抑制肺癌细胞增殖和转移的效应[4,5]。丙泊酚作为一种常用静脉麻醉药已被证实对人肺癌 A549 细胞的侵袭力有抑制作用[6]。但两者对肺癌细胞在体转移能力的影响尚不明确。本研究拟比较七氟醚吸入麻醉和丙泊酚静脉麻醉对老年肺癌根治术患者血清血管内皮生长因子(vascular endothelial growth factor, VEGF)、血管细胞黏附分子-1(vascular cell adhesion molecule-1, VCAM-1)、基质金属蛋白酶-2(matrix metalloproteinase-2, MMP-2)和 MMP-9 表达的影响,为临床麻醉用药提供参考。

1 对象与方法

1.1 对象

选择佛山市第一人民医院收治的美国麻醉医师协会(American Society of Anesthesiologists, ASA)Ⅰ~Ⅱ级择期全麻下行肺癌根治术患者 60 例,随机分为七氟醚组(S 组)和丙泊酚组(P 组),每组 30 例。所选患者满足以下条件:年龄 60~75 岁,无高血压、糖尿病、心脏病史,无贫血(Hgb > 12 g/L),无放化疗史,近 1 个月无麻醉镇痛药应用史。本研究经医院医学伦理委员会批准,所有患者或家属签署知情同意书。

1.2 方法

所有患者术前禁食 8 h,禁饮 4 h,均未术前用药。患者入室后常规面罩吸氧,氧流量为 5 L/min,用 Cicero EM 型麻醉机(Drager 公司,德国)监测血压(blood pressure, BP)、心率(heart rate, HR)、呼气末二氧化碳分压(end-tidal carbon dioxide partial pressure, $P_{et}CO_2$)、心电图(electrocardiogram, ECG)和脉搏血氧饱和度(pulse oxygen saturation, SpO_2),同时连接 Narcotrend(NT)麻醉深度监护仪(SCHILLER 公司,瑞士)。B 超辅助局麻下行右侧颈内静脉穿刺,并连续监测中心静脉压(central venous pressure, CVP)。术中控制补液速度为 8~10 ml/(kg·h),晶/胶体液比例为 1∶1,其中晶体液为乳酸林格液,胶体液为 6% 羟乙基淀粉液。麻醉诱导:静脉注射咪达唑仑 0.1 mg/kg,依托咪酯 0.25 mg/kg,舒芬太尼 0.5 mg/kg,维库溴铵 0.12 mg/kg,插入双腔支气管导管后行机械通气。S 组患者吸入七氟醚(批号:9301,丸石制药株式会社,日本)维持麻醉,患者七氟醚呼气末浓度维持在 1.7%~3.4%(1~2 MAC);P 组术中不吸七氟醚,静脉泵注丙泊酚(批号:LW216,阿斯利康,意大利)3~6 mg/(kg·h)。两组患者术中均静脉泵注瑞芬太尼 0.15~0.3 μg/(kg·min),氧流量为 2 L/min。术中维持平均动脉压(mean arterial pressure, MAP)上下波动不超过基础值 ±30%,CVP 6~12 cmH_2O,$P_{et}CO_2$ 35~45 mmHg,NT 值为40~50。术毕送患者到麻醉后恢复室(post anesthesia care unit, PACU)观察,监测 BP、HR、$P_{et}CO_2$、ECG、SpO_2。所有手术由同一组外科医师完成,所有患者麻醉由同一位有经验的麻醉医师完成。

分别于麻醉诱导前即刻(T0)、手术开始后 1 h(T1)、手术开始后 2 h(T2)、手术结束后 1 h(T3)、手术结束后 2 h(T4)抽取静脉血 2 ml(不含抗凝剂),离心分离血清并装于离心管中,编号密封放置于 -20℃冰箱中保存待查。采用酶联免疫吸附法检测两组患者血清 VEGF、VCAM-1、MMP-2 和 MMP-9 表达。VEGF、VCAM-1、MMP-2 和 MMP-9 试剂盒购自上海酶研生物科技有限公司,实验操作严格按试剂盒说明书进行。

1.3 统计学处理

采用 SPSS13.0 软件进行分析。正态分布的计量资料以均数 ± 标准差($\bar{x} \pm s$)表示,组间比较采用 t 检验,组内比较采用单因素方差分析,计数资料比较采用卡方检验。$P < 0.05$ 为差异有统计学意义。

2 结 果

2.1 两组患者基本资料

两组患者年龄、性别、体质量、ASA 分级、术中输液量、出血量、麻醉时间、术后病理分型及术中瑞芬太尼用量比较,差异无统计学意义($P > 0.05$;表 1)。

2.2 两组患者血清 VEGF、VCAM-1、MMP-2 和 MMP-9 水平

与 T0 时比较,S 组 T1~T4 时血清 VEGF 和 VCAM-1 表达明显降低($P < 0.05$),T2~T4 时 MMP-2 和 MMP-9 表达明显降低($P < 0.05$);P 组 T1~T4 时血清 VEGF、VCAM-1、MMP-2 和 MMP-9 表达无明显差异($P > 0.05$)。与 P 组比较,S 组 T2~T4时血清 VEGF、VCAM-1、MMP-2 和 MMP-9 表达明显降低($P < 0.05$;表 2)。

表 1 两组患者一般情况和术中各项指标比较

Table 1 Comparison of general condition and various intraoperative indices between two groups ($n=30$)

Item	Propofol group	Sevoflurane group
Gender(male/female, n/n)	19/11	21/9
Age(years, $\bar{x}\pm s$)	67 ± 7	68 ± 6
Body mass(kg, $\bar{x}\pm s$)	57 ± 3	55 ± 5
ASA(Ⅰ/Ⅱ, n/n)	13/17	14/16
Intraoperative rehydration fluids(ml, $\bar{x}\pm s$)	900 ± 170	980 ± 150
Intraoperative blood loss(ml, $\bar{x}\pm s$)	160 ± 50	190 ± 70
Anesthesia time(min, $\bar{x}\pm s$)	148 ± 25	153 ± 34
Pathological type(squamous carcinoma/adenocarcinoma, n/n)	25/5	23/7
Dosage of remifentanil(mg, $\bar{x}\pm s$)	1.9 ± 0.3	1.7 ± 0.4

ASA: American Society of Anesthesiologists

3 讨 论

研究证实,麻醉药物对肿瘤患者术后的长期生存和转归有一定影响。应用具有抑制肿瘤细胞生长和侵袭性的麻醉药物,可减少肿瘤细胞在手术期间的播散,减少肿瘤复发或转移的概率[7]。临床上常用吸入麻醉药浓度为 1 ~ 2 MAC,因此,本研究选择 1 ~ 2 MAC 的七氟醚维持麻醉。大量研究证实,肿瘤的发生、发展和转移依赖于肿瘤血管形成。肿瘤血管的形成受多种因子调控,VEGF 具有促进体内新生血管的生成、促进血管内皮细胞增殖、增加血管的通透性、维持血管的形态及完整性的作用,是目前发现的最重要的促进肿瘤血管形成的因子[8]。VCAM-1(CD106)属免疫球蛋白超家族,具有免疫球蛋白相似的分子结构,是 VLA4 的配体,内皮细胞受损后,VCAM-1 的表达增强。这些分子作用于微血管内皮细胞或白细胞,或者介导它们之间的相互作用,从而导致内皮及组织损伤和微循环障碍。目前发现,VCAM-1 参与了炎症调节反应、细胞和组织分化发育过程、免疫应答反应、淋巴细胞归巢和再循环以及肿瘤形成、扩散转移等过程[9]。MMP-2 和 MMP-9 是 MMP 家族中两个重要成员,属于 Zn^{2+} 和 Ca^{2+} 依赖的内源性蛋白水解酶类,能降解细胞外基质和基底膜主要结构蛋白为Ⅳ型胶原[10]。MMP-2 和 MMP-9 在肿瘤细胞浸润和转移中起着较为关键的作用,其表达水平高低与肺癌患者预后密切相关[11,12]。肿瘤细胞转移过程中,先分泌 MMP-2 和 MMP-9 降解Ⅳ型胶原,通过破坏基底膜和基膜构成的屏障而发生转移。

本研究发现,与术前相比,术中各时点丙泊酚组患者血清 VEGF、VCAM-1、MMP-2 和 MMP-9 的表达无明显差异,这与王宇娜等[13]研究结果相同。但是,加大丙泊酚剂量是否可以抑制由手术刺激引起的肺内弥漫性炎症细胞浸润、肺血循环障碍、肺毛细血管通透性增加等一系列变化导致的上述各因子生成的增加,尚不可知,有待进一步研究。以往尤华等[14]研究结果显示,丙泊酚比七氟醚更显著降低肺癌切除术患者血清 MMP-9 的表达,这与本研究结果不同,可能与本研究麻醉维持所用丙泊酚剂量较小有关。与 T0 时比较,S 组 T2 ~ T4 时 MMP-2 和 MMP-9 表达降低($P<0.05$),这与傅蕊等[15]研究结果相同。七氟醚组患者研究期间血清 VEGF、VCAM-1、MMP-2 和 MMP-9 的表达明显低于丙泊酚组,这可能与七氟醚在体内代谢途径有关。七氟醚在体代谢率为 5%,主要被细胞色素 P450 2E1 代谢,代谢产物对细胞功能有一定干扰[16]。由此推测,在体代谢率较高的七氟醚麻醉后,血清中含有较高的七氟醚代谢产物,对肺癌细胞分泌 VEGF、VCAM-1、MMP-2 和 MMP-9 有一定影响,但具体机

表 2 两组患者不同时点血清 VEGF、VCAM-1、MMP-2 和 MMP-9 水平的比较

Table 2 Comparison of VEGF, VCAM-1, MMP-2 and MMP-9 at different time points between two groups ($n=30, \bar{x}\pm s$)

Group	Index	T0	T1	T2	T3	T4
Propofol	VEGF(pg/ml)	433 ± 95	446 ± 77	439 ± 68	452 ± 53	443 ± 64
	VCAM-1(ng/ml)	258 ± 23	247 ± 28	269 ± 33	250 ± 24	261 ± 27
	MMP-2(ng/L)	321 ± 28	332 ± 22	316 ± 31	335 ± 28	346 ± 24
	MMP-9(ng/L)	356 ± 39	369 ± 32	361 ± 35	353 ± 29	371 ± 31
Sevoflurane	VEGF(pg/ml)	455 ± 78	449 ± 68 *	438 ± 57 *#	423 ± 61 *#	415 ± 60 *#
	VCAM-1(ng/ml)	266 ± 32	242 ± 23 *	251 ± 27 *#	245 ± 30 *#	240 ± 22 *#
	MMP-2(ng/L)	339 ± 27	341 ± 31	325 ± 26 *#	316 ± 22 *#	313 ± 27 *#
	MMP-9(ng/L)	365 ± 30	368 ± 27	352 ± 32 *#	348 ± 29 *#	345 ± 33 *#

VEGF: vascular endothelial growth factor; VCAM: vascular cell adhesion molecule; MMP: matrix metalloproteinase. T0: just before induction of anesthesia; T1: 1 h after surgery beginning; T2: 2 h after sugery beginning; T3: 1 h after the end of surgery; T4: 2 h after the end of surgery. Compared with T0, $^{*}P<0.05$; compared with propofol group, $^{\#}P<0.05$

制还有待进一步探讨。七氟醚吸入麻醉引起的上述各因子的变化可能会对肺癌患者术后复发及转归起到进一步改善作用,这仍有待进一步探讨。

综上所述,与丙泊酚静脉麻醉相比,七氟醚吸入麻醉能抑制老年肺癌根治术患者血清 VEGF、VCAM-1、MMP-2 和 MMP-9 的表达。

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