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· 论 著 ·

盐酸右美托咪定对食管癌根治术患者围术期血糖、 β -内啡肽、TNF- α 及 IL-6 表达的影响

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[摘要] **目的** 观察全麻期间持续应用盐酸右美托咪定对食管癌根治术患者围术期血糖、 β -内啡肽(β -EP)、肿瘤坏死因子 α (TNF- α)和白细胞介素6(IL-6)表达水平的影响。**方法** 40例择期行食管癌根治术的患者,所有患者均采用全凭静脉麻醉,随机分为盐酸右美托咪定组和对照组($n=20$)。两组分别于麻醉诱导前(T_0)、拔管(T_1)即刻、术后1d(T_2)和术后2d(T_3)晨抽取静脉血,测定血糖、血浆 β -EP、血清TNF- α 和IL-6水平。**结果** 与 T_0 点相比,对照组在 T_1 时点MAP和HR显著升高($P<0.05$), $T_1\sim T_3$ 时点血糖、血浆 β -EP浓度显著升高($P<0.05$), $T_1\sim T_2$ 时点血清TNF- α 和IL-6的浓度明显上升($P<0.05$);盐酸右美托咪定组在各时点均无明显变化,两组各时间点差异有统计学意义($P<0.05$)。**结论** 全麻期间持续应用盐酸右美托咪定可有效降低食管癌根治术患者围术期血糖、血浆 β -EP、血清TNF- α 和IL-6水平,抑制围术期应激反应。

[关键词] 盐酸右美托咪定;应激;血糖; β -内啡肽;肿瘤坏死因子 α ;白细胞介素6

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Effects of dexmedetomidine on blood glucose, β -endorphin, tumor necrosis factor- α and interleukin-6 in patients undergoing radical esophagectomy

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[Abstract] **Objective** To investigate the effects of dexmedetomidine on blood glucose, β -endorphin(β -EP), tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) levels in patients undergoing radical esophagectomy, and to discuss the possible mechanism. **Methods** Forty patients with esophageal carcinoma undergoing radical esophagectomy were randomly assigned to 2 groups: dexmedetomidine group and control group ($n=20$ in each). Blood samples were taken immediately before induction of anesthesia (T_0), immediately after tracheal extubation (T_1), day 1 and day 2 after operation (T_2, T_3) for determining the levels of blood glucose, plasma β -EP and serum TNF- α and IL-6. **Results** Compared with those at T_0 , MAP and HR at T_1 were significantly elevated ($P<0.05$) in the control group, the blood glucose and plasma β -EP at $T_1\sim T_3$ were significantly increased ($P<0.05$), and the serum TNF- α and IL-6 at T_1 and T_2 were significantly elevated ($P<0.05$). The blood glucose, plasma β -EP, serum TNF- α and IL-6 in dexmedetomidine group had no significant changes at all time points ($P>0.05$), and the above parameters were significantly different between the two groups at corresponding time points ($P<0.05$). **Conclusion** Continued application of dexmedetomidine can effectively decrease the levels of blood glucose, plasma β -EP, serum TNF- α and IL-6 in patients undergoing radical esophagectomy, inhibiting the peri-operative stress response.

[Key words] dexmedetomidine; stress; blood glucose; β -endorphin; tumor necrosis factor- α ; interleukin-6

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盐酸右美托咪定(dexmedetomidine)为新型高选择性 α_2 肾上腺素能受体激动剂,具有剂量依赖性的镇静催眠作用,还具有镇痛、抑制交感活性、改善手术期心血管稳定性等药理作用^[1],其对围术期应激反应和免疫功能可能具有一定的影响,但尚不明

确。因此,本研究对开胸手术患者全麻期间持续应用盐酸右美托咪定,观察患者围术期血糖、 β -内啡肽(β -EP)、肿瘤坏死因子 α (TNF- α)和白细胞介素6(IL-6)表达水平的改变,探讨其对围术期患者应激反应和免疫功能的影响,为后续研究奠定基础。

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1 资料和方法

1.1 一般资料 择期行食管癌根治术的患者40例,ASA I~II级,男19例,女21例,术前无感染、呼吸、免疫和内分泌系统疾病,未做放、化疗和输血治疗,亦未接受糖皮质激素等免疫抑制药治疗。所有患者均签署知情同意书。本研究得到医院伦理委员会批准。所有患者均采用全凭静脉麻醉,双盲、对照随机分为盐酸右美托咪定组和对照组($n=20$)。

1.2 麻醉方法 两组患者术前常规禁饮食。入室前30 min 肌内注射苯巴比妥钠0.1 g、阿托品0.5 mg。入室后局麻下行桡动脉及颈内静脉穿刺置管。盐酸右美托咪定组所有患者从麻醉诱导开始,15 min内静脉泵入剂量为 $1 \mu\text{g}/\text{kg}$ 的盐酸右美托咪定(批号:H20090248,江苏恒瑞医药股份有限公司),随后以 $0.2\sim 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ 维持,其维持的输注速率根据心率、血压等变化及时调整。两组患者均采用相同的麻醉诱导及维持方法:静脉注射咪达唑仑 $0.05 \text{ mg}/\text{kg}$ 、阿曲库铵 $0.6 \text{ mg}/\text{kg}$ 、芬太尼 $3 \mu\text{g}/\text{kg}$ 、普鲁泊福 $1 \text{ mg}/\text{kg}$,诱导后行气管插管、机械通气。潮气量(VT) $8\sim 10 \text{ ml}/\text{kg}$,频率(RR) $12\sim 14$ 次/min,维持PetCO₂于 $35\sim 40 \text{ mmHg}$ ($1 \text{ mmHg}=0.133 \text{ kPa}$)。持续泵入普鲁泊福($3\sim 6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$),瑞芬太尼($7\sim 12 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$),间断注射

阿曲库铵维持麻醉。术中SpO₂维持在98%以上,PetCO₂控制在 $30\sim 35 \text{ mmHg}$,吸入氧浓度(FiO₂) $0.8\sim 1.0$ 。两组患者连续监测ECG、MAP、HR、SpO₂、PetCO₂。两组患者术中均输注乳酸钠林格液和6%羟乙基淀粉,观察期间均不输库血和血制品。

1.3 观察指标及方法 两组患者均于麻醉诱导前(T₀)、拔管即刻(T₁)、术后1 d(T₂)和术后2 d(T₃)晨采取静脉血标本待检测。采用OneTouch II快速血糖仪测定血糖浓度。放射免疫分析法测定血浆 β -EP浓度,试剂盒购自北京华英生物技术研究所。酶联免疫双抗体夹心法检测血清TNF- α 和IL-6水平,试剂盒购自晶美生物工程(北京)有限公司。

1.4 统计学处理 采用SPSS 11.5软件,数据以 $\bar{x}\pm s$ 表示,组间同时间点数据采用配对 t 检验,组内数据采用重复方差分析的SNK检验,检验水平(α)为0.05。

2 结果

2.1 两组患者基线资料及围术期血流动力学的变化 结果(表1)表明,两组患者性别、年龄、体质量、麻醉时间、手术时间、术中失血量和尿量差异均无统计学意义。围术期血流动力学观察结果(表2)表明:与T₀点相比,对照组在T₁时间点MAP和HR升高($P<0.05$),盐酸右美托咪定组在各时间点均无明显变化;两组在T₁时间点差异具有统计学意义($P<0.05$)。

表1 两组患者围术期一般情况的比较

Tab 1 Clinical data of patients in two groups

($n=20$)

Group	Sex (female/male)	Age (year)	Body mass m/kg	Anesthesia time t/min	Operation time t/min	Blood loss V/ml	Urine volume V/ml
Dexmedetomidine	11/9	66.6 \pm 8.8	65.2 \pm 9.3	197.8 \pm 33.5	176.7 \pm 26.5	328.6 \pm 83.4	750.5 \pm 94.3
Control	10/10	68.4 \pm 10.6	67.8 \pm 7.5	210.1 \pm 28.6	190.8 \pm 31.4	340.8 \pm 92.5	740.9 \pm 86.4

表2 两组患者围术期血流动力学的变化

Tab 2 Perioperative hemodynamic changes in 2 groups

($n=20, \bar{x}\pm s$)

Index	Group	T ₀	T ₁	T ₂	T ₃
MAP p/mmHg	Dexmedetomidine	91.6 \pm 12.5	93.4 \pm 13.3 Δ	92.7 \pm 11.2	90.8 \pm 9.5
	Control	93.5 \pm 10.3	108.7 \pm 14.3*	94.6 \pm 12.1	92.2 \pm 11.3
HR f/min ⁻¹	Dexmedetomidine	80.2 \pm 12.6	83.4 \pm 11.1 Δ	82.2 \pm 10.9	81.1 \pm 9.3
	Control	83.6 \pm 13.1	99.6 \pm 16.1*	80.8 \pm 11.7	82.6 \pm 12.2

MAP: Mean arterial pressure; HR: Heart rate. T₀: Immediately before induction of anesthesia; T₁: Immediately after tracheal extubation; T₂, T₃: Day 1 and day 2 after operation. * $P<0.05$ vs T₀; Δ $P<0.05$ vs control group. $1 \text{ mmHg}=0.133 \text{ kPa}$

2.2 两组患者围术期血糖、 β -EP、TNF- α 及IL-6的变化 结果(表3)表明:与T₀点相比,对照组在T₁~T₃时点血糖、血浆 β -EP浓度升高($P<0.05$),

T₁~T₂时间点血清TNF- α 和IL-6的浓度明显上升($P<0.05$),并且高于盐酸右美托咪定组($P<0.05$);盐酸右美托咪定组在各时点均无明显变化。

表3 两组患者围术期血糖、β-内啡肽、TNF-α及IL-6的变化

Tab 3 Changes of perioperative blood glucose, β-EP, TNF-α and IL-6 in 2 groups

(n=20, $\bar{x} \pm s$)

Index	Group	T ₀	T ₁	T ₂	T ₃
Blood glucose c _B /(mmol · L ⁻¹)	Dexmedetomidine	4.87 ± 0.79	6.28 ± 0.66 [△]	6.03 ± 0.56 [△]	5.65 ± 0.68 [△]
	Control	4.66 ± 0.87	8.76 ± 0.74*	8.10 ± 0.65*	6.98 ± 0.53*
β-EP ρ _B /(pg · ml ⁻¹)	Dexmedetomidine	113.21 ± 11.46	129.11 ± 11.78 [△]	122.95 ± 12.28 [△]	116.56 ± 11.30 [△]
	Control	110.13 ± 11.55	163.54 ± 12.21*	158.03 ± 13.76*	135.92 ± 13.56*
TNF-α ρ _B /(ng · ml ⁻¹)	Dexmedetomidine	0.98 ± 0.46	1.35 ± 0.43 [△]	1.13 ± 0.53 [△]	1.02 ± 0.60
	Control	0.96 ± 0.56	2.34 ± 0.91*	1.66 ± 0.66*	1.22 ± 0.51
IL-6 ρ _B /(ng · ml ⁻¹)	Dexmedetomidine	66.3 ± 9.2	72.4 ± 10.1 [△]	69.8 ± 9.8 [△]	67.2 ± 9.6
	Control	65.7 ± 9.6	98.8 ± 13.1*	83.6 ± 10.5*	69.9 ± 8.9

* P < 0.05 vs T₀; [△] P < 0.05 vs control group

3 讨论

应激反应是指机体受到强烈刺激而发生的以交感神经兴奋和下丘脑-垂体-肾上腺皮质功能增强为主要特点的一种非特异性防御反应。术前患者的焦虑不安、恐惧失眠、术中麻醉和手术的侵袭,均可使下丘脑-垂体-肾上腺皮质轴系及交感神经-肾上腺髓质系统兴奋。因此,减轻应激可缓解机体的免疫抑制,降低术后并发症的发生率,改善高危患者的术后恢复^[2]。

β-内啡肽是具有免疫性的内源性阿片肽,在外界环境改变时启动下丘脑-垂体-肾上腺轴而发挥生物效应,同时β-内啡肽作为激素或神经介质参与机体系统功能的调节,并与应激反应的病理生理过程密切相关^[3]。因此,β-内啡肽是连接神经内分泌系统和免疫系统的“桥梁”^[4]。围术期患者血糖的变化同样是通过下丘脑-垂体-肾上腺轴而发挥作用的,且血糖变化程度与手术刺激强度正相关^[5]。本研究显示盐酸右美托咪定组的血糖和β-内啡肽浓度变化幅度小于对照组,说明全麻期间持续应用盐酸右美托咪定可能是通过对下丘脑-垂体-肾上腺轴的作用,从而减轻应激和缓解免疫抑制^[6]。

TNF-α是损伤早期出现增高的细胞因子,具有启动和触发炎症反应作用。IL-6是一种促炎性细胞因子,在应激状态下,IL-6可通过肾上腺素受体的介导促进促肾上腺皮质激素释放激素的分泌,进而激活下丘脑-垂体-肾上腺轴^[7]。两者是手术创伤后循环中主要的细胞因子,是活化的免疫细胞对损伤或感染应答的细胞外信号蛋白,其生物学效应极强,主要参与免疫应答和炎症反应。本研究发现对照组患者血清细胞因子含量随手术进程显著上升,盐酸右美托咪定组则无显著变化,组内和组间比较均有显著性。这表明盐酸右美托咪定可能使突触后受体激活,产生镇痛、镇静、降低交感活性,从而有效地抑制手术刺激引起的交感神经系统兴奋^[8]。

综上所述,全麻期间持续应用盐酸右美托咪定能有效维持血液动力学的稳定,降低围术期患者血糖、β-EP、TNF-α和IL-6水平的升高,一定程度上减轻了机体的应激,维持了细胞因子的相对平衡,缓解了免疫抑制,有利于食管癌根治术患者的术后恢复。

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