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右美托咪定对腹腔镜手术患者苏醒期血清皮质醇、醛固酮及炎症因子水平的影响 *

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摘要 目的：探讨腹腔镜手术(LS)应用右美托咪定(Dex)辅助麻醉对患者苏醒期血清皮质醇(COR)、醛固酮(ALD)及炎症因子水平的影响。**方法：**选取我院 2015 年 3 月 ~2017 年 3 月收治并择期行 LS 治疗的 138 例患者，采取随机数字表法均分为两组。所有患者均采取相同的常规静吸复合麻醉，观察组在此基础上于麻醉诱导前 15 min(T_0)静脉滴注负荷剂量为 1 μg/kg 的 Dex、而后以 0.5 μg/(kg·h)速度持续静脉泵注 Dex 至术毕前 10 min，对照组以等剂量生理盐水重复以上操作。记录比较两组 T_0 和拔管后 15 min (T_1)应激反应指标、炎症因子水平，麻醉苏醒期镇静 - 躁动评分(SAS)及术后不良反应的发生情况。**结果：**与 T_0 时相比，两组 T1 时血清 COR、ALD、CRP、TNF-α、IL-6 水平均显著升高(P<0.01)，且观察组以上指标均显著低于对照组(P<0.01)。观察组麻醉苏醒期 SAS 评分为(2.96± 0.32)分，显著低于对照组【(4.14± 0.38)分】(P<0.01)。观察组术后不良反应率为 4.3%，较对照组(15.9%)明显降低(P<0.05)。**结论：**应用右美托咪定辅助麻醉更能有效降低腹腔镜手术患者苏醒期应激反应，抑制机体炎症反应，提高苏醒质量，且安全性高。

关键词：腹腔镜手术；右美托咪定；苏醒期；应激反应；炎症因子

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Effects of Dexmedetomidine on Serum Levels of Cortisol, Aldosterone and Inflammatory Factors in Recovery Period of Patients Undergoing Laparoscopic Surgery*

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ABSTRACT Objective: To investigate the effects of dexmedetomidine (Dex) on the levels of serum cortisol (COR), aldosterone (ALD) and inflammatory cytokines of patients undergoing laparoscopic surgery (LS). **Methods:** 138 patients treated with LS in our hospital from March 2015 to March 2017 were selected and equally divided into two groups with the method of random number table. All the patients were treated with the same conventional inhalation anesthesia, on the basis of which, the observation group were injected with intravenous drip loading dose of 1 μg/kg Dex 15min (T_0) before the anesthesia induction, and then continuous intravenous infusion of Dex at the speed of 0.5 μg/ (kg·h) to preoperative the 10 min. The control group was given the same dose of saline following the above induction. The stress response index, inflammatory factor levels, the sedation agitation scale (SAS) and the adverse reaction were recored and compared between the two groups at T_0 and 15 min after the extubation (T_1). **Results:** Compared with those at T_0, the serum COR, ALD, CRP, TNF-α and IL-6 levels of both groups at T_1 were significantly increased(P<0.01), which were significantly lower in the observation group than those of the control group (P<0.01). The SAS score of observation group was (2.96± 0.32) during the anesthesia recovery period, which was significantly better than that of the control group (4.14± 0.38, P<0.01). The incidence rate of adverse reaction in the observation group was 4.3%, which was significantly lower than that of the control group (15.9%, P<0.05). **Conclusion:** Dexmedetomidine assisted anesthesia could effectively reduce the stress reaction of patients undergoing laparoscopic surgery during the recovery period, inhibit the inflammatory response and improve the quality of recovery with high safety.

Key words: Laparoscopic surgery; Dexmedetomidine; Recovery period; Stress response; Inflammatory factors

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前言

腹腔镜手术(laparoscopic surgery，LS)是近年来临床应用最为广泛的微创术式，具有术野清晰、恢复快、痛苦小、切口小等

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优点[1],但患者仍不可避免地遭受手术操作与人工气腹所带来的损伤,引发应激与炎症反应,从而影响手术质量[2]。静吸复合麻醉是目前应用较为普遍的全身麻醉 (general anesthesia,GA)方式,其特点是麻醉诱导快、麻醉深度可控性较强、苏醒迅速等,但患者苏醒期易出现躁动,不利于病人术后机体功能恢复[3]。因此,在 LS 过程中为最大限制度的降低手术创伤应激对患者机体造成的伤害,临床须制定出更为有效、合理的麻醉方案。

右美托咪定(dexmedetomidine,Dex)属 α2- 肾上腺素受体(α2-adrenergic receptor,α2-AR)激动剂,具有抗交感神经、抗焦虑、镇静镇痛等作用,现已大量应用于全麻手术中[4,5]。近年来有研究表明 Dex 还具有抗炎作用[6]。本研究以我院 2015 年 3 月~2017 年 3 月收治并择期行 LS 治疗的患者为研究对象,探讨 LS 应用 Dex 辅助麻醉对患者苏醒期皮质醇(cortisol,COR)、醛固酮(aldosterone,ALD)及炎症因子水平的影响,以期为 LS 围术期麻醉管理提供参考依据。现报道如下。

1 资料与方法

1.1 一般资料

选取我院 2015 年 3 月 ~2017 年 3 月收治并择期行 LS 治疗的 138 例患者,采取随机数字表法均分为两组。纳入标准:① 年龄 18~60 岁;② 无麻醉禁忌证,美国麻醉医师协会(ASA)分级为Ⅰ~Ⅱ级[7];③ 无 LS 禁忌证,手术类型为腹腔镜阑尾切除术(LA)、子宫肌瘤剔除术(LM)、腹腔镜胆囊切除术(LC),各类手术均顺利完成;④ 身体质量指数(BMI)≤ 30 kg/m²;⑤ 麻醉时间≤ 120 min,手术时间≤ 90 min,气腹时间 <60 min,术中输液量 <1000 mL;⑥ 苏醒时间≤ 25 min,拔管时间≤ 30 min;⑦ 自愿受试,签署知情同意书;⑧ 近期未有镇痛药、镇静剂、β 受体阻滞剂等有关药物应用史;⑨ 临床资料完整。排除标准:① 既往有精神病、代谢性疾病、消化性溃疡、慢性疼痛、肾脏病等病史者;② 术前明显紧张焦虑者;③ 合并呼吸系统疾病(如肺结核、支气管炎、哮喘病等)、心脏病(如心肌炎、高血压性心脏病、心动过缓、风湿性心脏病等)、糖尿病、高血压等疾患者;④ 伴有凝血功能、肝功能障碍者;⑤ 过敏体质或对本研究药物过敏者;⑥ 哺乳或妊娠期妇女。本研究经我院医学伦理委员会审查同意。两组基线资料、手术情况对比差异均无统计学意义(P>0.05),具有临床可比性。见表 1~2。

表 1 两组基线资料的比较

Table 1 Comparison of the baseline information between two groups

Groups	n	Age(year)	BMI(kg/m²)	ASA classification(case)	
				Grade Ⅰ	Grade Ⅱ
Observation group	69	35.6± 5.4	22.5± 2.3	36	33
Control group	69	36.3± 5.1	22.3± 2.1	34	35
P		0.435	0.595	0.734	

表 2 两组手术情况的比较

Table 2 Comparison of the operation situation between two groups

Groups	n	Operation type(case)			Operation time(min)	Pneumoperitoneum time (min)	Anesthesia time(min)	Intraoperative transfusion volume(ml)	Wake-up time(min)	Extubation time(min)
		LA	LM	LC						
Observation group	69	24	26	19	60.4± 9.8	45.6± 8.4	84.8± 12.1	814.6± 57.2	18.5± 3.2	20.6± 3.8
Control group	69	24	22	23	61.3± 10.2	44.9± 8.7	82.7± 12.3	802.8± 58.5	18.1± 3.5	21.1± 3.7
P		0.700			0.598	0.631	0.314	0.233	0.485	0.435

1.2 麻醉方法

两组患者均采取相同的常规静吸复合麻醉,具体如下 1)所有患者均给予相同的术前准备,入室后建立外周静脉通路(PVC),常规监测脑电双频指数(BIS)、心电图(ECG)、心率(HR)、脉搏血氧饱和度(SpO_2)、血压(BP)等。2)麻醉诱导:① 用药方案:舒芬太尼 (0.5 μg/kg)+ 咪达唑仑 (0.02 mg/kg)+ 罗库溴铵(0.6 mg/kg)+ 丙泊酚(2 mg/kg),静脉输注;② 患者均于满意的肌松条件与麻醉深度(BIS 为 50~55)下行气管插管,妥善固定后连接麻醉机;③ 设置参数:吸呼比(I:E)为 1:2,氧流量 2 L/min,吸入氧浓度(FiO_2)100%,呼吸频率(RR)12 次 /min,潮气量(VT)6~8 ml/Kg,呼气末二氧化碳分压 ($PETCO_2$) 为 30~40 mmHg(1 mmHg=0.133 kPa)。3)麻醉维持:① 用药方案:吸入 3%七氟醚 +2~4 L/min 氧流量;② 术中维持 BIS 为 40~55,并同时注意维持肌松(可间断静脉推注适量罗库溴铵)。观察组:在此基础上,加用 Dex(辰欣药业股份有限公司,国药准字 H20130027)辅助麻醉;具体是于麻醉诱导前 15 min,将负荷剂量为 1 μg/kg 的 Dex 以静脉滴注的方式输注 10 min,而后以 0.5 μg/(kg·h)速度持续静脉泵注至手术结束前 10 min。对照组:在常规静吸复合麻醉基础上,以等剂量生理盐水重复以上操作。

1.3 观察指标

1)血清指标测定:① 所有患者均于麻醉诱导前 15 min(T_0)和麻醉苏醒期[拔管后 15 min(T_1)]各抽取 4 mL/ 次的肘静脉血,离心分离血清,均分为两份(一份用于检测 COR、ALD 水平,另一份用于测定炎症因子水平)保存于 -80℃冰箱中待检;② 应激指标(COR、ALD)和炎症因子[C 反应蛋白(CRP)、肿瘤坏死因子(TNF)-α、白细胞介素(IL)-6]均运用酶联免疫法检测,仪器采用全自动酶标仪(美国伯乐,型号 680),试剂盒均购自德国 Roche

公司;① 上述各指标检测步骤均严格参照配套说明书执行。2) Ricker 镇静 - 躁动评分(SAS)标准[8]:共分为 7 级(以 1~7 分表示),依次为不能唤醒(1 分)、深度镇静(2 分)、镇静(3 分)、安静合作(4 分)、躁动(5 分)、非常躁动(6 分)、危险躁动(7 分)。3)术后不良反应情况:对术后每位患者因麻醉药物而引起的不良反应 / 事件(如恶心呕吐、呼吸抑制、寒战、躁动等)进行详细记录。

1.4 统计学分析

采取统计软件 SPSS19.0 处理数据,计量资料以 ($\bar{x}\pm s$)表示,应用 t 检验,计数资料以(%)表示,采用 x^2 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组麻醉苏醒期应激反应指标的比较

与 T_0 时间点对比,两组 T_1 时血清 COR、ALD 水平均显著升高(P<0.01),且观察组较对照组均显著更低(P<0.01),见表 3。

表 3 两组 T_0、T_1 时应激反应指标的比较($\bar{x}\pm s$)

Table 3 Comparison of the stress response index between two groups at T_0 and T_1($\bar{x}\pm s$)

Groups	n	COR(nmol/L)			ALD(ng/L)		
		T_0	T_1	P	T_0	T_1	P
Observation group	69	375.3± 49.4	529.4± 63.5	0.000	68.9± 8.7	106.5± 12.8	0.000
Control group	69	371.8± 51.2	657.8± 74.2	0.000	66.7± 9.1	173.9± 16.7	0.000
P		0.683	0.000		0.149	0.000	

2.2 两组麻醉苏醒期血清炎症因子水平的比较

两组 T_1 时血清 CRP、TNF-α、IL-6 水平较 T_0 时均显著上升(P<0.01),但与对照组同期相比,观察组 T_1 时以上指标均显著更低(P<0.01),见表 4。

表 4 两组 T_0、T_1 时血清炎症因子水平的比较($\bar{x}\pm s$)

Table 4 Comparison of the serum inflammatory factors between two groups at T_0 and T_1($\bar{x}\pm s$)

Groups	n	CRP(mg/L)			TNF-α(ng/L)			IL-6(μg/L)		
		T_0	T_1	P	T_0	T_1	P	T_0	T_1	P
Observation group	69	28.9± 4.2	43.6± 6.7	0.000	21.8± 3.5	27.9± 4.1	0.000	15.4± 2.3	26.5± 3.7	0.000
Control group	69	30.1± 4.4	59.8± 7.5	0.000	22.7± 3.6	41.8± 5.9	0.000	14.9± 2.1	39.6± 5.3	0.000
P		0.104	0.000		0.139	0.000		0.185	0.000	

2.3 两组麻醉苏醒期 SAS 评分的比较

观察组麻醉苏醒期 SAS 评分为(2.96± 0.32)分,显著低于对照组【(4.14± 0.38)分】(P=0.000)。

2.4 两组术后不良反应发生情况的比较

观察组术后有 2 例恶心呕吐,1 例心动过缓;对照组出现 2 例呼吸抑制,3 例恶心呕吐,4 例躁动,2 例心动过缓。观察组不良反应率为【4.3%(3/69)】,较对照组【15.9%(11/69)】相比明显降低(P=0.024)。

3 讨论

在 GA 诱导期及苏醒期中,气管插管与拔管操作均可对患者造成强烈的刺激,尤其是拔管时应激反应十分剧烈,患者极易出现躁动、呕吐反射、呛咳反射等不适,引起心律失常、BP 升高、HR 加快,并可引发神经内分泌系统[如下丘脑 - 垂体 - 肾上腺轴(HPA)、交感 - 肾上腺髓质系统等]功能明显变化,更甚者可出现脑血管意外、心搏停止等不良事件[9]。为此,在 LS 时应选择较为理想的麻醉管理方案(既能保证麻醉质量,又可避免因麻醉过浅所致的严重并发症及麻醉过深而引发的苏醒延迟等)以减轻应激源对病人机体的损伤、提高手术安全性。

Dex 属镇静催眠药,对α2-AR 具有高选择性,可增强迷走神经活动、抑制交感神经(SN)冲动发放,且不产生明显呼吸抑制[10]。当前,Dex 已作为辅助用药应用于重症监护病人和行 GA 手术患者机械通气与气管插管时的镇静。研究表明[11]Dex 的药代动力学特性为静滴后分布半衰期(t1/2α)约为 6 min、稳态分布容积(Vdss)约为 118L、消除半衰期(t1/2)约为 2 h、起效时间约为 10~15 min。鉴于 Dex 的起效时间,本研究 Dex 的应用时机定于麻醉诱导前 15 min。研究[12]显示 Dex 的镇静镇痛效果具有一定剂量依赖性。佟凯[13]研究发现结直肠癌 LS 患者麻醉维持阶段采用小剂量[0.2 μg/(kg·h)]Dex 辅助麻醉时苏醒期易出现躁动、大剂量[0.8 μg/(kg·h)]Dex 镇静效果虽突出但又易诱发苏醒延迟,但中剂量[0.5 μg/(kg·h)]Dex 既能维持合适的镇静深度,又能避免苏醒延迟的发生,提高手术质量。张涛等[14]研究指出在后腹腔镜术 GA 诱导前 10 min 内将 1 μg/kg 负荷剂量的 Dex 以静脉泵入后再续以 0.5 μg/(kg·h)持续泵入辅助麻醉能有效抑制病人围术期应激反应。由此可见,本研究制定的辅助麻醉方案[麻醉诱导前 15 min 采取 Dex(1 μg/kg)静脉滴注 + 麻醉维持阶段以 0.5 μg/(kg·h)静脉持续泵注]是有一定理论与实践基础的。

手术应激反应可导致 HPA 功能增强、交感 - 肾上腺髓质系统过度兴奋。COR 属类激素,由肾上腺于应激反应下产生,其作用是维持正常生理机能,COR 机体含量具有反映 HPA 功能的作用[15]。ALD 属盐皮质激素家族一员,亦由肾上腺皮质细胞分泌,是肾素 - 血管紧张素系统(RAS)的一部分[16]。本研究结果显示采取 Dex 辅助麻醉的观察组麻醉苏醒期血清 COR、ALD 水平均显著低于予以常规静吸复合麻醉的对照组同期,这与蒙丽宇[17]报道相似,提示 LS 患者采用 Dex 辅助麻醉更能

有效抑制苏醒期应激反应。究其原因可能与 Dex 能和位于蓝斑核(LC)上的 α2-AR 有效结合,进而抑制去甲肾上腺素(NE)合成与释放、降低 HPA 活化程度,从而起到良好的中枢镇静效果有关[18]。有研究显示机体炎症反应的发生与患者生命体征变化、组织损伤等有关,炎性状态也是 GA 苏醒期躁动的重要因素[19]。CRP 为急性相蛋白,能有效反映机体炎症、创伤状态[20]。TNF-α 为促炎细胞因子,主要由单核细胞(MC)、巨噬细胞(Mac)等分泌产生,当机体处于急性感染或创伤时可迅速合成与分泌,并可直接介导组织损伤、诱发炎症级联反应[21]。IL-6 属趋化因子家族成员之一,具有急性期反应、调节免疫应答等多种生物效应,其机体含量能反映组织损伤程度[22]。本研究结果显示:与对照组同期相比,观察组麻醉苏醒期血清 CRP、TNF-α、IL-6 水平均显著更低;这与张静贻[23]研究结果相似,说明采用本 Dex 辅助麻醉方案更有助于减轻 LS 患者机体炎症反应。分析原因可能为 Dex 能通过抑制 COR、儿茶酚胺等介质释放,下调 MC、Mac 等分泌炎性细胞因子的能力,发挥抗炎作用。本研究中,与对照组(4.14± 0.38)对比,观察组麻醉苏醒期 SAS 评分为(2.96± 0.32)分,显著更优,提示采取 Dex 辅助麻醉更能显著预防 LS 患者苏醒期躁动、提高苏醒质量。这可能与 LS 患者围术期机体应激反应与炎症反应的有效控制关系密切。从术后不良反应的角度分析,本研究结果显示:与对照组(15.9%)相比,观察组术后不良反应率仅为 4.3%,明显下降,且未见严重不良反应 / 时间,与相关报道一致[24,25]。由此可见,Dex 辅助麻醉方案只要掌握合理的用法与用量是安全有效的。

综上所述,应用右美托咪定辅助麻醉更能有效降低腹腔镜手术患者苏醒期应激反应、抑制机体炎症反应,提高苏醒质量,且安全性高。但对于右美托咪定辅助麻醉方案的具体作用机制及有效性、安全性仍应开展更多临床研究进一步论证与分析。

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