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多点针刺对全麻下行微创 LC 术后患者胃肠功能及血清 NO、MPO、HSP90、OXA 水平变化的影响 *

曲立哲¹ 白冬¹ 孙瑜¹ 俞红丽¹ 王燕颖^{2△}

(1 上海中医药大学附属市中医医院麻醉科 上海 200071; 2 同济大学附属东方医院特诊部 上海 200120)

摘要 目的:探讨多点针刺对全麻下行腹腔镜胆囊切除术(LC)后患者胃肠功能及血清一氧化氮(NO)、髓过氧化物酶(MPO)、热休克蛋白90(HSP90)、食欲素A(OXA)水平的影响。**方法:**选取2018年9月~2020年9月我院全麻腹腔镜胆囊切除术(LC)的患者107例,采用随机数字表法,将其分为针刺组(n=55例)及对照组(n=52例)。对照组术后给予常规治疗;观察组在对照组基础上给予多点针刺,时间分别为:术前30分钟(采血后)、术后4-6小时、术后两天,每日两次,每次留针30 min;取穴为双侧三阴交、足三里、上巨虚、内关、合谷、百会、印堂穴。检测两组术前30分钟(针刺前)、术后30分钟、术后第3 d的血清NO、MPO、HSP90、OXA水平的变化;记录术后第一次肛门排气时间、第一次肛门自主排便时间、肠鸣音的恢复时间,观察术后48 h恶心呕吐、腹痛、腹泻等发生情况。**结果:**术后30 min,与术前相比较,NO、MPO、HSP90升高,OXA下降,差异有统计学意义($P<0.05$);术后第3 d,与术后30 min相比较,NO、MPO、HPS90下降,观察组水平较对照组低,差异均有统计学意义($P<0.05$);术后第3 d,与术后30 min相比,NO、MPO、HSP90降低,观察组水平较对照组高,且差异有统计学意义($P<0.05$)。术后48 h,观察组腹胀、恶心呕吐及腹痛的发生率明显低于对照组,差异有统计学意义($P<0.05$)。结论:多点针刺可显著促进全麻LC术后胃肠功能恢复,加快术后腹胀、恶心呕吐及腹痛缓解;显著降低全麻LC术后患者血清NO、MPO、HSP90水平,升高血清OXA水平。我们推测,OXA信号通路增强,可能是多点针刺治疗全麻LC术后胃肠功能紊乱神经内分泌免疫调节机制中的一个靶点。

关键词:多点针刺; NO; MPO; HSP90; OXA; 胃肠功能

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Effects of Multi-point Acupuncture on Gastric Function and Serum NO, MPO, HSP90 and OXA Levels in Patients after Minimally Invasively Laparoscopic Cholecystectomy Surgery under General Anesthesia*

QU Li-zhe¹, BAI Dong¹, SUN Yu¹, YU Hong-li¹, WANG Yan-ying^{2△}

(1 Department of Anesthesiology, Shanghai Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, 200071, China; 2 Department of Special Diagnosis, East Hospital, Tongji University, Shanghai, 200120, China)

ABSTRACT Objective: To investigate the effects of multi-point acupuncture on gastrointestinal function and serum levels of nitric oxide (NO), myeloperoxidase (MPO), heat shock protein 90(HSP90) and orexin A (OxA) in patients undergoing laparoscopic cholecystectomy (LC) under general anesthesia. **Methods:** A total of 107 patients undergoing laparoscopic cholecystectomy (LC) under general anesthesia in our hospital from September 2018 to September 2020 were selected and divided into acupuncture group (n=55) and control group (n=52) by random number table method. The control group was given routine treatment after surgery. The observation group was additively given multi-point acupuncture on the basis of the control group, and the time was: 30 minutes before surgery (after blood collection), 4-6 hours after surgery, and two days after surgery, twice a day, each time for 30 min; The acupoints selected are bilateral Sanyinjiao, Zusanli, Shangjuxu, Neiguan, Hegu, Baihui and Yintang. The serum levels of NO, MPO, HSP90 and OXA in both groups were detected 30 minutes before the operation (before acupuncture), 30 minutes after the operation, and 3 days after the operation. The time of the first anal exhaust after surgery, the time of the first anal voluntary defecation, and the recovery time of intestinal sounds were recorded. The occurrence of nausea, vomiting, abdominal pain, diarrhea and other conditions 48 hours after surgery were observed. **Results:** 30 min after operation, compared with before operation, NO, MPO, HSP90 increased, OXA decreased, the differences were statistically significant ($P<0.05$). On the third day after surgery, compared with 30 min after surgery, NO, MPO and HPS90 decreased, and the levels in the observation group were lower than those in the control group, the differences were statistically significant ($P<0.05$). On the 3rd day after

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作者简介:曲立哲(1971-),女,硕士,副主任医师,主要研究方向:麻醉与围术期康复,E-mail:13761003275@139.com

△ 通讯作者:王燕颖(1972-),女,主任医师,博士,主要研究方向:功能性胃肠病与身心疾病,

E-mail:yanyingwang1972@163.com,电话:13918809377

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surgery, compared with the 30 min after surgery, OXA level in the observation group was higher than that in the control group, and the differences were statistically significant ($P<0.05$). 48 hours after operation, the incidence of abdominal distension, nausea, vomiting and abdominal pain in the observation group was significantly lower than that in the control group, the differences were statistically significant ($P<0.05$). The first postoperative defecation time and bowel sound recovery time of the observation group were shorter than those of the control group, and the differences were statistically significant ($P<0.05$). **Conclusion:** Multi-point acupuncture can significantly promote the recovery of gastrointestinal function, and accelerate the relief of abdominal distension, nausea, vomiting and abdominal pain after LC general anesthesia. The serum levels of NO, MPO and Hsp90 were significantly decreased, and the serum level of OXA was increased in patients after LC under general anesthesia. We speculated that the enhancement of OXA signaling pathway may be a target in the neuroendocrine immune regulation mechanism of gastrointestinal dysfunction after multi-point acupuncture in the treatment of LC under general anesthesia.

Key words: Multi-point acupuncture; Nitric oxide; Myeloperoxidase; Heat shock protein 90; Orexin A; Gastrointestinal function

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前言

全麻手术过程中气腹及腹腔镜手术产生的应激反应均会对患者免疫功能造成不同程度的影响,通常表现为免疫抑制^[1]。腹部术后胃肠功能紊乱是由于刀口疼痛、精神紧张、手术过程对消化道神经血管的刺激或损伤等所致,术后出现类似胃肠神经官能症、肠麻痹的各种症状^[2,3]。李小华等对针刺对腹部术后胃肠功能紊乱的疗效进行Meta分析,结果提示,针刺对于腹部术后在缩短患者术后首次肛门排气、排便时间以及肠鸣音恢复时间方面具有优势^[4],但关于其机制尚不清楚。本研究对多点针刺治疗对全麻腹腔镜胆囊切除术(Laparoscopic cholecystectomy, LC)后胃肠功能紊乱的恢复进行疗效评价,并观察术前、术后30分钟、术后3天血清一氧化氮(nitric oxide, NO)、髓过氧化物酶(Myeloperoxidase, MPO)、热休克蛋白90(Heat shock protein 90, HSP90)、食欲素A(orexin-A, OXA)水平的变化;旨在为多点针刺治疗全麻下LC术后胃肠功能紊乱的机制提供理论基础和研究方向。

1 材料与方法

1.1 病例来源及分组

选取上海市中医医院2018年9月至2020年9月之间全麻下行LC术治疗的患者107例,采用随机数字表法分为观察组及对照组;收集两组患者性别、合并基础疾病、年龄等资料。观察组55例,对照组52例。本研究严格遵循赫尔辛基宣言伦理原则。所有患者充分了解本研究内容并签署知情同意书。

1.2 纳入标准

纳入标准:①经B超、CT或MRI检查诊断为胆囊结石;②年龄在18到70岁之间;③符合LC手术指征。

1.3 排除标准

④合并恶性肿瘤、肝硬化、严重脏器功能不全等;⑤合并腹膜炎、自身免疫性疾病、腹腔严重黏连等;⑥合并抑郁症、认知障碍、精神分裂症等;⑦依从性差者。

1.4 治疗方法

所有患者均全麻下行LC术。术前完善相关检查,了解患者基本情况,积极治疗基础疾病,做好术前准备;麻醉常规诱导后行气管插管,麻醉维持采用静吸复合,术中监测生命体征。术

中病人取仰卧位,头高足低15~20℃,左侧倾斜15℃,LC术采用标准三孔操作法,于脐下缘一长10~15 mm的弧形切口,第二孔选择镰状韧带与肝前缘交界处的剑突下体表投影处,肝圆韧带右侧插入(肝缘下),第三孔选择胆囊底部相应体表部位。建立12~14 mmHg压力的CO₂气腹后,分离胆囊周围正常组织及粘连,依次结扎胆囊动脉、引出胆总管及切除胆囊,经主操作孔取出切除的胆囊。

对照组:按照上述LC术流程进行常规治疗;术后给予常规护理、补液、禁食、预防感染等对症支持治疗。

观察组:在对照组基础上给予多点针刺,术前30分钟(采血后)、术后4~6小时、术后两天每日两次,每次留针30 min。所有针刺操作均由具有主治及以上职称针灸科医师完成。患者均取穴为:双侧三阴交、足三里、上巨虚、内关、合谷、百会、印堂穴。具体针刺操作方法为:患者取仰卧位,准确定位三阴交、足三里、上巨虚、内关、合谷、百会、印堂穴位,局部使用75%医用酒精棉球消毒,选择长度适宜“华佗牌不锈钢毫针”,采用平补平泻手法,局部得气即可。

1.5 观察指标

检测血清NO、MPO、HSP90、OXA水平:分别于两组术前30分钟(针刺前)、术后30分钟、术后第3天,检测血清NO、MPO、HSP90、OXA水平;采用酶联免疫吸附法,所有试剂盒由武汉伊莱瑞特生物科技有限公司生产。

胃肠功能恢复情况:记录所有患者术后肠鸣音的恢复时间(术后6 h开始,每2 h听诊1次肠鸣音,肠鸣音为≥4次/分为肠鸣音恢复)、首次肛门排气时间、首次肛门自主排便时间。

并发症:观察两组患者术后48小时,是否存在腹痛、恶心呕吐、腹泻、切口感染等并发症发生。

1.6 统计学方法

数据分析采用SPSS 20.0软件,计数资料以率(%)表示,采用 χ^2 检验进行组间对比;计量资料使用($\bar{x} \pm s$)表示,采用t检验;以 $P<0.05$ 为有显著性差异。

2 结果

2.1 两组患者基线资料比较

两组性别、年龄、基础疾病等比较,差异无统计学意义($P>0.05$);具体见表1。

表 1 两组患者基线资料比较

Table 1 Comparison of baseline data between the two groups

| Groups | n | Male/female | Age($\bar{x} \pm s$, y) | Body mass index ($\bar{x} \pm s$, kg/m ²) | Calculi | Diabetes yes/no | Hypertension yes/no | Hyperlipaemia yes/no |
|-------------------|----|-------------|---------------------------|--|---------|--------------------|------------------------|-------------------------|
| Observation group | 55 | 24/31 | 46.71± 7.29 | 25.26± 2.42 | 28/27 | 8/47 | 17/38 | 6/49 |
| Control group | 52 | 22/30 | 46.84± 7.78 | 25.01± 2.50 | 27/25 | 8/44 | 16/36 | 7/45 |

2.2 两组术后血清 NO、MPO、HSP90、OXA 比较

与术前相比较,两组术后 30 分钟 NO、MPO、HSP90 水平升高,OXA 水平均下降,差异有统计学意义($P<0.05$);与术后 30 min 相比较,两组术后第 3d NO、MPO、HPS90 水平均下降,针

刺组水平较对照组低,差异均有统计学意义($P<0.05$);术后第 3 d,与术后 30 min 相比较,两组 OXA 水平均明显升高,针刺组水平较对照组高,且差异有统计学意义($P<0.05$)。具体见图 1-4。

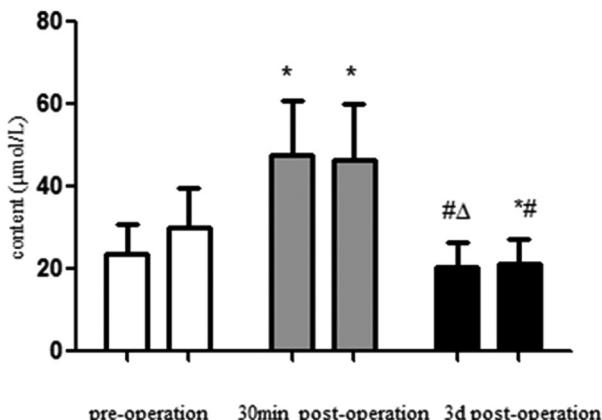


图 1 两组术前、术后 30 min、术后 3 d 血清 NO 水平比较

Fig.1 Comparison of serum NO levels between the two groups before

surgery, 30 min after surgery and 3 d after surgery

Note: * $P<0.05$, compared with preoperative; # $P<0.05$, compared with 30 min after treatment; ^ $P<0.05$, compared with control group.

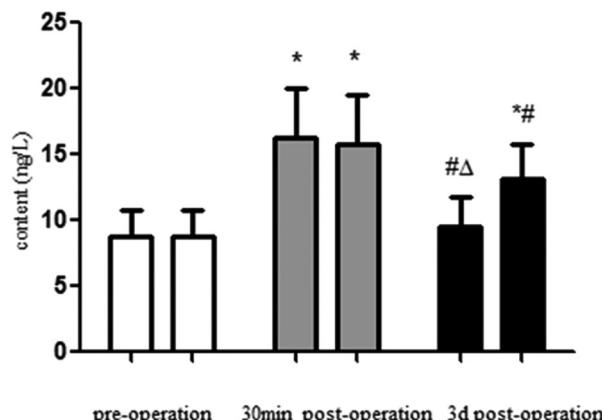


图 2 两组术前、术后 30 min、术后 3 d 血清 MPO 水平比较

Fig.2 Comparison of serum MPO levels between the two groups before

surgery, 30 min after surgery and 3 d after surgery

Note: * $P<0.05$, compared with preoperative; # $P<0.05$, compared with 30 min after treatment; ^ $P<0.05$, compared with control group.

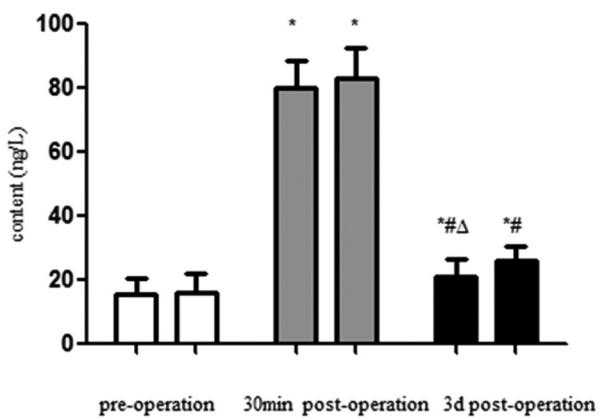


图 3 两组术前、术后 30 min、术后 3 d 血清 HPS90 水平比较

Fig.3 Comparison of serum HPS90 levels between the two groups before

surgery, 30 min after surgery and 3 d after surgery

Note: * $P<0.05$, compared with preoperative; # $P<0.05$, compared with 30 min after treatment; ^ $P<0.05$, compared with control group.

2.3 两组术后胃肠功能恢复情况比较

观察组术后首次排气时间、首次排便时间、肠鸣音恢复时间较对照组短,差异有统计学意义($P<0.05$);具体见图 5。

2.4 两组术后并发症比较

术后 48 小时,观察组腹胀、恶心呕吐及腹痛的发生率明显

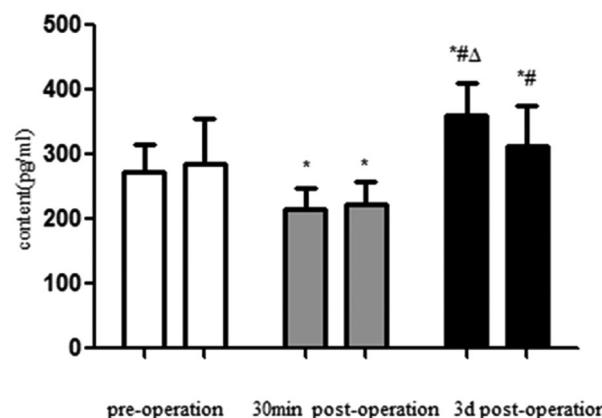


图 4 两组术前、术后 30 min、术后 3 d 血清 OXA 水平比较

Fig.4 Comparison of serum OXA levels between the two groups before

surgery, 30 min after surgery and 3 d after surgery

Note: * $P<0.05$, compared with preoperative; # $P<0.05$, compared with 30 min after treatment; ^ $P<0.05$, compared with control group.

高于对照组,差异有统计学意义($P<0.05$);观察组及对照组腹泻肌创口感染发生率差异无统计学意义($P>0.05$)。具体见表 2

3 讨论

针刺作为传统医学的重要部分,特点是无毒副作用、操作

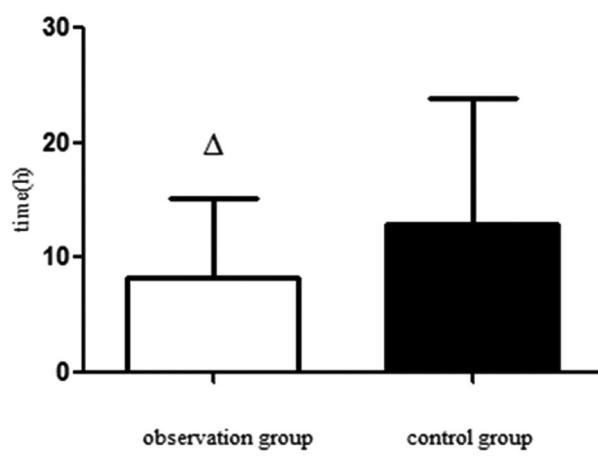


图 5 两组术后肠鸣音恢复时间比较

Fig.5 Comparison of postoperative bowel sound recovery time between the two groups

Note: $^{\triangle} P < 0.05$, compared with control group.

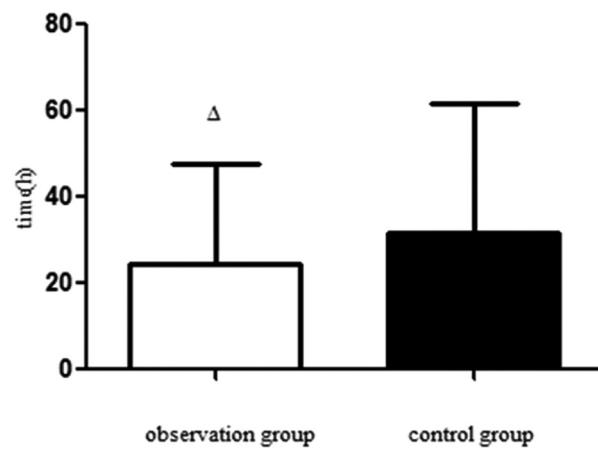


图 7 两组术后首次排便时间比较

Fig.7 Comparison of first postoperative defecation time between the two groups

Note: $^{\triangle} P < 0.05$, compared with control group.

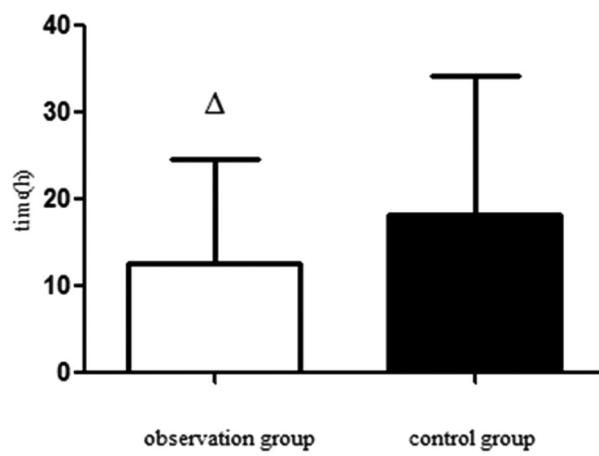


图 6 两组术后首次排气时间比较

Fig.6 Comparison of the first postoperative exhaust time between the two groups

Note: $^{\triangle} P < 0.05$, compared with control group.

简便、成本低廉等。针刺可调节脑肠轴功能活动,促进脑肠肽(如P物质、血管活性肠肽等)合成和释放,达到促进消化道腺体分泌、改善胃慢波节律运动障碍、促进胃排空及胃肠平滑肌蠕动等作用^[5,6]。本研究结果表明,多点针刺缩短首次排气排便及肠鸣音恢复时间,加快术后腹胀、恶心呕吐及腹痛缓解,降低术后48小时腹胀发生率;与前期Meta分析结果一致。针刺对减轻全麻术后患者胃肠功能紊乱的发生率、提高患者生活质量具有积极作用。

全麻术后脾胃气机失调,气血瘀滞,经络不通,针刺阳明经可补益后天之气,扶正祛邪,气血生、经脉荣;足三里具有补中益气、培元固本的作用^[7];针刺合谷有通达三焦气机,调整脏腑气血,疏肝理气,健脾扶正,疏通经络等作用^[8]。内关穴属于厥阴经腧穴,多血少气,调节全身气机,从阴引阳的特点^[9]。阳明与厥阴为气机升降枢纽,调整阴阳,脏腑化生。足三里及上巨虚均为下合穴,可达和胃止痛、疏调气机、胀消痛止、调达气机之功。

表 2 两组术后并发症比较[例(%)]

Table 2 Comparison of postoperative complications between the two groups [cases (%)]

| Groups | Abdominal distension | Nausea and vomiting | Abdominal pain | Diarrhea | Wound infection | Abdominal distension; |
|-------------------|----------------------|---------------------|-----------------|----------|-----------------|-----------------------|
| Observation group | 10 [△] | 8 [△] | 12 [△] | 2 | 0 | 0 [△] |
| Control group | 19 | 16 | 22 | 3 | 1 | 6 |

Note: $^{\triangle} P < 0.05$, compared with control group.

效^[10]。足三里和三阴交分属胃脾经,脾胃为后天之本、气血生化之源,二穴一表一里,一阴一阳,一脏一腑,针刺可补益后天之本,充养周身气血,调节中焦气机升降^[11]。百会穴居巅顶,内通于脑,为督脉要穴,连贯周身经穴,通达阴阳脉络^[12];印堂为经外奇穴,位于督脉之上。针刺百会、印堂穴可调节肝胆气血运行,达到疏肝醒神、和胃降逆之功效;可引起皮质兴奋性改变^[13]。

中医学认为,全身麻醉和手术创伤可致气机紊乱、脑失所养、神机不运;而胆为中正之官,主决断,与情绪关系密切。肝胆相表里,胆囊切除术后肝失疏泄、肝气郁结,升降失调。脑为元神之府,肠为浊物归处,《伤寒杂病论》中多言谵语与阳明病,肠

中有燥屎有关,是中医学对脑与胃肠关联的佐证。脑神支配胃肠运化水谷,胃肠将吸收的精微补散于脑,二者升降协调,机体才能有序运转,此为中医的脑肠相通^[14]。陈姝等研究结果表明,针刺足三里、内关等穴位,刺激信号经脊髓到达孤束核,整合后上行投射激活下丘脑室旁核,由室旁核-延髓背侧迷走复合体-迷走神经通路进行下行投射,经迷走神经到达靶器官-胃,以神经传导及神经内分泌等方式对胃肠的功能活动进行调节^[15]。

本研究结果提示,术后3d,与术后30 min相比较,两组OXA水平均明显升高,针刺组水平较对照组高。OXA是兴奋性下丘脑神经肽激素的合称,是一种脑肠肽,参与各种自主神

经控制的内分泌功能通路^[16]。下丘脑 OXA 神经元可投射至大脑的各个区域, OXA 受体主要分布在结肠肌间神经丛、纵肌层和黏膜层, 检测外周 OXA 水平可反映胃肠道组织内 OXA 受体含量^[17]。既往研究表明, PET-CT 及功能磁共振显示针刺不同穴位可激活不同脑区核团递质和神经肽的释放^[18]; 如胡伟等通过功能磁共振成像发现, 针刺足三里可激活下丘脑和海马等脑区^[19]。全麻和手术应激时 OXA 神经元的化学活化依赖于多巴胺, 并随着中脑 - 皮层 - 边缘神经传递而增强^[20]; OXA 诱导中脑腹侧被盖区多巴胺神经元的兴奋性突触的可塑性变化, 导致多巴胺的大量释放, 本研究结果表明术后多点针刺增加 OXA 水平, 机体的兴奋和应激能力增强, 达到改善胃肠道功能等作用。

本研究结果提示, 与术前相比较, 两组术后 30 分钟 NO 水平均明显升高; 与术后 30 min 相比较, 两组术后第 3d NO 水平均下降, 针刺组水平较对照组低。NO 体现机体氧化应激水平, 参与多种信号转导通路, 在维持血管、呼吸系统、免疫系统和神经系统的生理功能中发挥重要作用^[21]。生理浓度 NO 具有神经保护作用, 维持神经系统的生理功能; 高浓度 NO 则抑制脑部交感神经活性。本研究中, 术后 30 分钟 NO 水平增高, 针刺组 3 d 后明显下降, 表明多点针刺抑制 NO 的高表达可能是术后胃肠功能恢复进程的有效方式。

麻醉及手术均能明显抑制机体的免疫功能。本研究结果提示, 与术前相比较, 两组术后 30 分钟 MPO 水平均明显升高; 与术后 30 min 相比较, 两组术后第 3d MPO 水平均下降, 针刺组水平较对照组低。MPO 主要生成次氯酸、亚硝基阴离子、羟自由基等, 在中枢神经系统, MPO 主要表达于激活的星形胶质细胞, 释放炎症因子对多巴胺能神经元功能造成损伤^[22]。针刺刺激穴位深层感受器的神经末梢, 可能通过激活神经内分泌免疫调节网络, 减少 MPO 表达, 调节脑肠轴功能活动。

HSP90 是一种应激蛋白, 当机体受到全麻和手术应激时, HSP90 会被机体大量合成并分泌出来, 激活免疫系统引起多种信号转导的改变, 抗自由基减轻外界刺激对细胞的损伤^[23,24]。本研究结果提示, 与术前相比较, 两组术后 30 分钟 HSP90 水平均明显升高; 与术后 30 min 相比较, 两组术后第 3d HSP90 水平均下降, 针刺组水平较对照组低。HSP90 水平在术后 30min 表达增加, 以抵制应激刺激对细胞的损伤; 随着术后时间推移而进一步下降, 与 NO、MPO 水平呈正相关, 而多点针刺进一步加强此效应。可以推测, HSP90 可能是 NO、MPO 调节的协同伴侣, 机制可能依赖于 HSP90 ATP 酶水解的调节^[25]。HSP90 水平的变化与 OXA 水平变化呈负相关, 可能由于应激诱导 HSP90 结构域组织高磷酸化, 而 OXA 并不依赖 HSP90 来实现自身的折叠和稳定性。

最近的研究证实, 全身麻醉中用到的异丙酚显著降低丘脑、大脑皮质、下丘脑等葡萄糖代谢率; 下丘脑则是执行神经内分泌免疫的高级中枢^[26]。本研究观察到, 与对照组比较, 针刺组血清中 OXA 水平升高显著, 血清中 NO、MPO、HSP90 水平降低显著。我们推测, 全麻和手术增加了氧化损伤的易感性, 抑制 OXA 的神经肽数量或灵敏度。多点针刺通过启动“穴位 - 经络 - 中枢 - 胃肠道”互动机制: 调控中枢及外周 OXA 的升高的表达, 来降低 NO、MPO、HSP90 的表达和协同作用, 恢复应激后

脏腑的生理功能以及阴阳气血平衡, 使全麻和手术致紊乱的胃肠功能重新恢复正常^[27,28]。研究表明, 抑制中脑腹侧背盖区的多巴胺能神经元, 可阻断大鼠 OXA 神经末梢所产生的觉醒效应, 提示中脑腹侧背盖区的多巴胺神经元介导了 OXA 调控的促进觉醒效应^[29,30]。OXA 信号通路增强, 可能是多点针刺治疗全麻 LC 术后胃肠功能紊乱神经内分泌免疫机制中一个的靶点。

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