

doi: 10.13241/j.cnki.pmb.2020.02.029

地佐辛对骨关节病髋关节置换术患者炎症应激反应及认知功能的影响*

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摘要 目的:探讨地佐辛对骨关节病髋关节置换术(THA)患者术后炎症应激反应及认知功能的影响。**方法:**选取汉中市中心医院2017年1月至2018年12月收治的97例骨关节病行THA患者,采用随机数字法将其分为观察组(n=49例)对照组(n=48例)。观察组患者术前20 min给予地佐辛2.5 mg。对照组患者术前20 min给予0.9%氯化钠作为安慰剂。对比术前及术后1h、6h、12h两组白细胞介素(IL-6)、肿瘤坏死因子-α(TNF-α)水平、肾上腺素及皮质醇水平;术前、术后1d、3d、7d采用简易智力精神状态检查量表(MMSE)对所有患者认知功能进行评定并行组间比较,记录两组不良反应发生情况。**结果:**术前两组IL-6、TNF-α水平差异无统计学意义($P>0.05$),观察组术后1h、6h、12h IL-6水平、术后12h TNF-α水平低于对照组,差异均有统计学意义($P<0.05$)。术前两组肾上腺素及皮质醇水平差异无统计学意义($P>0.05$),观察组术后12h肾上腺素及术后6h、12h皮质醇水平低于对照组,差异均有统计学意义($P<0.05$)。术前及术后7d两组MMSE评分差异无统计学意义($P>0.05$),观察组术后1d及3d MMSE评分明显高于对照组,差异均有统计学意义($P<0.05$)。两组不良反应发生率差异无统计学意义($P>0.05$)。**结论:**地佐辛可显著降低骨关节病患者行THA术后炎症因子水平,改善术后应激状态,保护患者认知功能,且患者安全耐受,具有一定的临床应用价值。

关键词:地佐辛;骨关节病;髋关节置换术;炎症因子;应激状态;认知功能

中图分类号:R684 **文献标识码:**A **文章编号:**1673-6273(2020)02-342-04

Effects of Dezocine on Inflammatory Stress Response and Cognitive Function in Patients with Bone and Joint Disease Undergoing Total hip Arthroplasty*

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ABSTRACT Objective: To investigate effects of dezocine on postoperative inflammatory stress response and cognitive function in patients with bone and joint disease undergoing total hip arthroplasty (THA). **Methods:** 97 cases of bone and joint disease patients undergoing THA from January 2017 to December 2018 who were treated in Hanzhong Central Hospital were selected. The patients were divided into the observation group (n=49) and the control group (n=48) according to random number table. The observation group were given dezocine 2.5 mg 20 min before operation, while the control group were given 0.9% sodium chloride as a placebo. The levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), adrenaline and cortisol were compared before and 1h, 6h, 12h after operation. Simple Mental State Examination Scale (MMSE) was used to assess the cognitive function of all patients before operation, 1d, 3d and 7d after operation, and the results were compared between groups. The incidence of two groups of adverse reactions were recorded. **Results:** There were no significant differences in the levels of IL-6 and TNF-α between the two groups before operation ($P>0.05$). The levels of IL-6 and TNF-α at 1h, 6h, 12h after operation in the observation group were lower than those in the control group, the difference was statistically significant ($P<0.05$). There were no significant differences in adrenaline and cortisol levels between the two groups before operation ($P>0.05$). The level of adrenaline at 12h after operation and cortisol at 6h and 12h after operation in observation group were significantly lower than those in control group, the differences were statistically significant ($P<0.05$). There was no significant difference in MMSE score between the two groups before and on the 7d after operation ($P>0.05$), while the MMSE score of the observation group on the 1d and 3d after operation was significantly higher than that of the control group, the differences were statistically significant ($P<0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Dezocine can effectively reduce the level of inflammatory cytokines in bone and joint disease patients after total hip arthroplasty, improve postoperative stress state and protect their cognitive function, and patients are safe to tolerate, which has a certain clinical value.

Key words: Dezocine; Bone and joint disease; Total hip arthroplasty; Inflammatory cytokines; Stress state; Cognitive function

Chinese Library Classification(CLC): R684 **Document code:** A

Article ID: 1673-6273(2020)02-342-04

* 基金项目:陕西省卫生计生委科研基金项目(2015B1106)

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(收稿日期:2019-04-28 接受日期:2019-05-24)

前言

人工髋关节置换术(THA)常用于骨关节炎、股骨头坏死等髋关节疾病的治疗,利用生物相容性较高的特殊金属材料制成类人体关节,替换病变组织,以达到缓解疼痛、清除病灶、恢复关节活动、改善关节功能等目的^[1-3]。基于术式创伤大、术中出血量多、老年人基础疾病多等原因,术后易出现强烈疼痛,伴发机体高应激反应及炎症因子的瀑布样过度释放^[4-6]。术后认知功能障碍(POCD)是以焦虑、精神错乱、人格改变以及记忆受损^[7]等为主要表现的术后中枢系统功能障碍。疼痛可直接诱导中枢神经系统及外周组织炎症反应,刺激机体产生疼痛应激反应。各种细胞因子和免疫介质可加重疼痛反应,进一步促进应激激素释放^[8,9]。疼痛、炎症反应、应激三者可通过复杂的神经-体液系统相互作用,产生交联放大作用。过度应激和炎症反应可诱发加剧 POCD^[10-12]。研究显示全身炎症反应综合征及各种细胞因子的释放,小胶质细胞的炎性反应可严重影响 POCD 的发生和发展^[13]。因此,减轻 THA 患者术后疼痛,抑制炎症及应激反应,从而减少认知功能的损害是临床研究的关键。本研究旨在探究地佐辛对骨关节炎 THA 患者炎症应激反应及认知功能的影响,为临床治疗提供指导。

1 资料与方法

1.1 一般资料

选取汉中市中心医院 2017 年 1 月至 2018 年 12 月收治的 97 例骨关节炎 THA 患者,纳入标准:各种原发性或继发性骨关节炎、类风湿性关节炎、股骨颈囊内骨折、髌臼骨折、脱位、创伤性骨关节炎、股骨头无菌性坏死、某些类型的骨肿瘤、慢性炎症性髋关节病损等造成髋关节严重疾患,伴有疼痛,关节活动受限,影响日常生活,且非手术治疗无法缓解症状者,符合髋关节置换手术指征,具有自主意识,无相关手术禁忌,并签署手术知情同意书。排除标准:局部或其他部位尚有活动性感染,严重肝肾功能障碍及心肺功能不全者,妊娠及哺乳期患者,气道阻塞或呼吸抑制者,严重骨质疏松,关节周围肌肉麻痹,难以保持术后关节稳定者,全身情况或伴发疾病使人难以耐受置换,阿片类药物过敏者。采用随机数字法将其分为观察组($n=49$)和对照组($n=48$)。其中观察组男 26 例,女 23 例;年龄 55~75 岁,平均(61.98 ± 4.89)岁;体重 47~71kg,平均(58.28 ± 5.08)kg;学历水平:小学及小学以下 16 例,中学 25 例,大专及大专以上 8 例。对照组男 25 例,女 23 例;年龄 58~73 岁,平均(62.26 ± 5.01)岁,体重 50~69kg,平均(58.32 ± 4.89)kg;学历水平:小学及小学以下 17 例,中学 24 例,大专及大专以上 7 例。两组性别、年龄、体重及学历等基线资料对比,差异无统计学意义($P>0.05$),具备可比性。本研究获汉中市中心医院伦理委员会审核同意。

1.2 方法

两组均予以 meda Datex/s 监护仪监测血压及血氧饱和度,建立静脉通路,舒芬太尼(厂家:宜昌人福药业有限责任公司,国药准字:H20054171,规格:按 $C_{22}H_{30}N_2O_2$ 计 1 mL:50 μ g)0.3 μ g/kg,静脉滴注,诱导麻醉;丙泊酚(厂家:四川国瑞药业有限责任公司,国药准字:H20040079,规格:10 mL:0.1 g)

4 μ g/mL 靶控输注,1 mg/kg 罗库溴铵(厂家:浙江华海药业股份有限公司,国药准字:H20183264,规格:5 mL:50 mg)松弛肌肉后行气管内插管;丙泊酚浓度 3 μ g/mL、芬太尼(厂家:宜昌人福药业有限责任公司,国药准字:H20030200,规格:按 $C_{20}H_{28}N_2O_5$ 计 5 mg)0.05~0.15 μ g/kg $\cdot$ min 维持麻醉。观察组患者手术结束前 20 min 给予地佐辛(厂家:扬子江药业集团有限公司,国药准字:H20080329,规格:1 mL:5 mg)2.5 mg,静脉滴注。对照组患者手术结束前 20 min 给予 0.9%氯化钠作为安慰剂。术后均予以静脉自控镇痛(PCA),药物配比:芬太尼 10 μ g/kg,昂丹司琼(厂家:辰欣药业股份有限公司,国药准字:H20067241,规格:2 mL:4 mg(按 $C_{18}H_{19}N_3O$ 计)8 mg 及生理盐水共配制成 100 mL,背景输注 2 mL/h,PCA 量 2 mL,锁定时间 15 min。

1.3 观察指标

1.3.1 炎症因子检测 分别于术前、术后 1h、6h、12h 抽取患者静脉血 4 mL,未经抗凝,1000 r/min 离心 15 min 后取血清,采用酶联免疫法(ELISA)检测各个时间点白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)水平,所用试剂盒由加拿大 YYES 公司生产,严格遵守试剂盒操作进行。

1.3.2 认知功能评价 于术前、术后 1d、3d、7d 采用简易智力精神状态检查量表(MMSE)对所有患者认知功能进行评定^[14],评分和术前相比下降 ≥ 2 分则提示认知功能降低,并可诊断为 POCD。27-30 分为正常,21-26 分为轻度智能障碍;10-20 分为中度智能障碍,0-9 为重度智能障碍,分值越高表明患者认知功能越好。

1.3.3 肾上腺素及皮质醇检测 术前、术后 1h、6h、12h 抽患者静脉血 4 mL 置于肝素抗凝管,3000 转/min,离心 5 min,取血浆,分 2 份,一份采用高效液相色谱仪(日本 Shimadzu LC-10AD 泵,L-ECD6A 电化学检测器)检测肾上腺素水平。同一时间抽静脉血 4 mL,37 度孵育制成血清,采用 ACCESS 全自动化学发光酶免分析仪(贝克曼公司)测定皮质醇水平。

1.3.4 安全性评价 记录两组不良反应发生情况。

1.4 统计学方法

采用 SPSS19.0 统计分析软件处理数据,组间计数资料行 χ^2 检验,计量资料符合正态性、方差齐性时行 t 检验,如不符合正态分布,则行 Wilcoxon 秩和检验分析。以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者术前、术后 1h、6h、12h 炎症因子比较

术前两组 IL-6、TNF- α 水平差异无统计学意义($P>0.05$),观察组术后 1h、6h、12h IL-6 水平以及术后 12h TNF- α 水平低于对照组,差异均有统计学意义($P<0.05$),见表 1。

2.2 两组患者术前、术后 1h、6h、12h 肾上腺素及皮质醇比较

术前两组肾上腺素及皮质醇水平差异无统计学意义($P>0.05$),观察组术后 12h 肾上腺素及术后 6h、12h 皮质醇水平低于对照组,差异均有统计学意义($P<0.05$),见表 2。

2.3 两组患者术前、术后 1d、3d、7d MMSE 评分比较

术前及术后 7d 两组 MMSE 评分差异无统计学意义($P>0.05$),观察组术后 1d 及 3d MMSE 评分明显高于对照组,差异

均有统计学意义($P<0.05$),见表3。

表1 两组患者术前、术后1h、6h、12h炎症因子比较($\bar{x}\pm s$)

Table 1 Comparison of inflammatory cytokines before operation, 1h, 6h and 12h after operation between the two groups ($\bar{x}\pm s$)

Groups	IL-6(pg/mL)				TNF- α (pg/mL)			
	Before operation	1h after operation	6h after operation	12h after operation	Before operation	1h after operation	6h after operation	12h after operation
Observation group(n=49)	4.71 $\pm$ 2.55	14.60 $\pm$ 4.65	85.53 $\pm$ 27.73	63.47 $\pm$ 19.35	3.02 $\pm$ 1.53	4.13 $\pm$ 1.40	4.79 $\pm$ 1.65	4.84 $\pm$ 1.95
Control group (n=48)	4.46 $\pm$ 2.97	17.28 $\pm$ 5.84	107.69 $\pm$ 29.20	80.92 $\pm$ 22.04	3.65 $\pm$ 1.47	3.84 $\pm$ 1.05	5.38 $\pm$ 2.24	5.93 $\pm$ 1.87
t	0.444	2.497	3.831	4.141	2.168	1.156	1.475	2.810
P	0.658	0.014	0.000	0.000	0.061	0.251	0.144	0.006

表2 两组患者术前、术后1h、6h、12h等时间点肾上腺素及皮质醇比较($\bar{x}\pm s$)

Table 2 Comparison of adrenaline and cortisol before operation, 1h, 6h and 12h after operation between the two groups ($\bar{x}\pm s$)

Groups	Adrenaline(pg/mL)				Cortisol(ng/mL)			
	Before operation	1h after operation	6h after operation	12h after operation	Before operation	1h after operation	6h after operation	12h after operation
Observation group(n=49)	49.65 $\pm$ 15.63	54.48 $\pm$ 15.91	55.17 $\pm$ 11.73	65.81 $\pm$ 17.53	71.33 $\pm$ 19.28	111.19 $\pm$ 42.82	207.58 $\pm$ 60.25	142.67 $\pm$ 39.86
Control group (n=48)	48.16 $\pm$ 14.75	55.47 $\pm$ 18.69	56.91 $\pm$ 12.39	79.47 $\pm$ 16.98	74.38 $\pm$ 22.38	120.84 $\pm$ 36.62	245.92 $\pm$ 74.40	183.17 $\pm$ 76.29
t	0.483	0.281	0.710	3.898	0.719	1.194	2.786	3.267
P	0.630	0.779	0.479	0.000	0.474	0.236	0.007	0.002

表3 两组患者术前、术后1d、3d、7d认知功能评分比较($\bar{x}\pm s$,分)

Table 3 Comparison of cognitive function scores before operation, 1d, 3d and 7d after operation between the two groups ($\bar{x}\pm s$, scores)

Groups	Before operation	1d after operation	3d after operation	7d after operation
Observation group(n=49)	28.02 $\pm$ 1.53	26.13 $\pm$ 1.40	27.71 $\pm$ 1.55	28.02 $\pm$ 1.53
Control group(n=48)	27.86 $\pm$ 1.49	24.26 $\pm$ 1.66	25.58 $\pm$ 1.74	28.60 $\pm$ 1.65
t	0.455	5.992	6.369	1.796
P	0.651	0.000	0.000	0.759

2.4 两组治疗期间不良反应发生情况比较

观察组发生不良反应有头晕头痛2例,恶心呕吐3例、尿潴留2例,不良反应率14.28%(7/49);对照组头晕头痛2例,恶心呕吐2例,不良反应发生率为8.33%(4/48),两组对比差异无统计学意义($\chi^2=2.103$, $P=0.087$)。

3 讨论

THA临床广泛应用于多种骨关节疾病的治疗,由于手术创伤面积大,手术时间长,术中出血多等因素,患者术后易合并术后疼痛、严重炎症及应激反应^[14-16]。POCD可表现为焦虑、精神错乱、人格改变以及记忆受损等多种中枢神经功能障碍,严重影响临床预后及疗效^[17]。研究显示疼痛可引机体内分泌炎症因子释放,刺激交感神经兴奋,肾上腺素及皮质醇分泌增加,诱导机体应激反应,过度应激和炎症反应可诱发加剧POCD^[18]。有效缓解骨关节病患者THA术后疼痛,减少炎症、应激反应是减少认知功能的损害的关键。

地佐辛是一种阿片受体激动-拮抗药,主要通过兴奋 κ 受体,抑制缓激肽释放,降低损伤部位痛觉感受器的敏感性并阻断痛觉向中枢传导,减少突触前神经递质释放,使脊髓后神经元突触超极化抑制,降低中枢神经元兴奋性,发挥较强的镇痛效果,对 μ 受体具有不同程度的兴奋-拮抗作用,因此具有阿片类镇痛作用但不产生明显的恶心呕吐、呼吸抑制等药物副反应,药物依赖性较少^[19,20]。本研究显示,观察组采用地佐辛镇痛治疗后,术后1h、6h、12h IL-6水平、术后12h TNF- α 水平低于对照组,术后12h肾上腺素及6h、12h皮质醇水平低于对照组,提示地佐辛可有效降低炎症细胞因子及肾上腺素、皮质醇表达水平,减轻炎症反应及应激反应。其机制可能是术中及术后伤害性刺激促进组织痛觉神经元传入冲动增加,刺激神经末梢及神经元中降钙素基因相关肽(CGRP)的表达,可与巨噬细胞、淋巴细胞、肥大细胞等多种免疫细胞相互作用,促进IL-6、TNF- α 等炎症因子释放^[21,22]。这些细胞因子可进一步刺激CGRP的分泌,二者相互促进,形成炎症介质的级联效应。同时炎症因子可

通过复杂的信号交联系统刺激肾上腺素及皮质醇等应激激素合成分泌,诱导机体应激反应,形成正反馈通路,加重对机体的损害。地佐辛可通过激动 κ 受体,降低外周及中枢神经元痛觉敏感性,减少痛觉冲动传入,从而减少 CGRP 表达,抑制痛觉-炎症,炎症介质-应激激素相互放大效应^[23,24]。

POCD 是指患者在术后或麻醉后出现精神状态、社交活动、认知功能以及人格等变化,患者可出现记忆力、注意力、社交能力、语言理解能力的损害或降低^[25]。研究显示^[26],炎症介质可刺激神经胶质细胞活化,诱导中枢神经退行性病变,引起认知功能下降。围手术期中枢神经源性炎症反应,外周血液中促炎因子比如 IL-1 β 、TNF- α 、IL-6 等水平升高,促使中枢神经胶质细胞活化,在 POCD 的产生中发挥重要作用^[27]。本研究显示,研究组术后 1d 及 3d 认知功能评分明显优于对照组,提示地佐辛可显著改善患者术后认知功能。主要可能通过以下几方面发挥作用:1.地佐辛通过其显著镇痛作用,减少 CGRP 的表达分泌,抑制 CGRP 直接介导的神经源性炎症反应,减少痛觉过敏及中枢神经源性炎症反应,抑制胶质细胞活化,减少神经细胞退行性改变,从而保护认知功能^[28];2.抑制 CGRP 与 IL-6、TNF- α 等相互作用,抑制外周免疫细胞活化及各种炎性相关介质释放,减少外周炎性因子经血脑屏障进入中枢诱发中枢炎症反应^[29];3. IL-6 等炎症细胞因子表达水平与应激激素表达水平呈正相关,二者经复杂网络系统互相作用,抑制应激激素表达水平可有效抑制炎症反应,抑制二者相互正反馈刺激作用,从而减轻神经系统损失,保护认知功能^[30]。两组不良反应差异无统计学意义,说明地佐辛不会增加不良反应,安全可行。

综上所述,地佐辛可有效降低骨关节病 THA 患者炎症因子及应激激素水平,保护患者认知功能,且患者安全耐受,值得临床应用推广。

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