doi: 10.13241/j.cnki.pmb.2017.02.024

氟比洛芬酯对食管癌患者围术期外周血淋巴细胞亚群的影响

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摘要 目的：探究氟比洛芬酯对食管癌患者围术期外周血淋巴细胞亚群的影响。**方法：**选择 2014 年 6 月 ~2016 年 8 月期间在我院择期行食管癌根治术患者 72 例为研究对象，采用随机数字法将其分为氟比洛芬酯组（39 例）和对照组（33 例），患者均给予常规麻醉处理，对照组患者泵入 5 mg 托烷司琼与 20 μg/kg 芬太尼；氟比洛芬酯组患者给予氟比洛芬酯 2 mg/kg。评价术后 12 h、24 h 和 48 h 患者疼痛情况（VAS 评分），并于术前 1 h、术后 24 h、术后 72 h 检测患者血清 T 细胞中 $CD3^+$、$CD4^+$、$CD8^+$ 及 $CD56^+$ 比例。**结果：**两组患者术后不同时刻 VAS 评分比较，差异均无统计学意义（P>0.05）；术后 24 h 两组患者 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均显著降低（P<0.05），术后 72 h 两组患者 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平均升高，且氟比洛芬酯组患者恢复到术后 1 h 水平，而对照组患者均仍低于术后 1 h，且术后 72 h 氟比洛芬酯组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均高于对照组，差异均有统计学意义（P<0.05），而 $CD8^+$ 与 $CD56^+$ 比例在两组各个时点均没有变化（P>0.05）；两组患者均未发生严重不良反应。**结论：**食管癌患者在手术过程中均出现免疫抑制，氟比洛芬酯麻醉效果较好，且对机体免疫功能具有保护作用，促进手术患者免疫功能的恢复，具有重要的临床价值。

关键词：氟比洛芬酯；食管癌；淋巴细胞亚群

中图分类号：R735.1 **文献标识码：**A **文章编号：**1673-6273（2017）02-298-03

Effect of Flurbiprofen Axetil on Patients with Esophageal Cancer Perioperative Peripheral Blood Lymphocyte Subsets

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ABSTRACT Objective: To explore the effect of flurbiprofen axetil on patients with esophageal cancer perioperative peripheral blood lymphocyte subsets. **Methods:** 72 cases of the radical operation of esophageal cancer in our hospital were selected as study subjects from June 2014 to August 2016; They were randomly divided into flurbiprofen group(39 cases)and control group(33 cases), which were given anesthesia treatment; The control group of patients with infusion of 5mg tropisetron and fentanyl 20 g/kg; flurbiprofen group were given flurbiprofen 2 mg/kg. To evaluation of postoperative pain in patients with 12 h, 24 h, and 48 h, and to detect the proportion of $CD3^+$, $CD4^+$, $CD8^+$ and $CD56^+$ in serum lymphocytes of patients on Preoperative 1 h, 24 h after operation, and postoperative 72 h. **Results:** The VAS score of patients in both groups had no statistically difference at different times (P>0.05); The level of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ in both groups had significantly reduced(P<0.05) on 24 h moments and the level of $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ was elevated on 72 h moments; And flurbiprofen group were restored to the level of 1 h after operation, while the control group were still lower than that of moment; And the level of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ in flurbiprofen group were higher than the control group on 72 h moments(P<0.05); And the level of $CD8^+$ and $CD56^+$ in two groups at each point of time has no change(P>0.05); No serious adverse reactions occurred in the two groups. **Conclusion:** Immune suppression occurs in patients with esophageal cancer during the operation; Flurbiprofe's anesthesia effect is good, and it has protective effect on immune function of organism, and promote the recovery of immune function in patients with surgery, which has important clinical value.

Key words: Flurbiprofen axetil; Esophageal cancer; Lymphocyte subsets

Chinese Library Classification(CLC): R735.1 Document code: A

Article ID: 1673-6273(2017)02-298-03

前言

食管癌是一种消化系统恶性肿瘤，既往报道[1]，每年食管癌的发病约 50 万人，有 30 万人发生死亡。而我国是食管癌的高发国家，每年超过 15 万人因食管癌发生死亡，且我国食管癌的 5 年生存率低于 10%，严重影响我国居民的生命安全[2]。既往报

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（收稿日期：2016-10-12 接受日期：2016-10-31）

道[3,4],肿瘤患者的病情进展与机体免疫功能存在密切联系,肿瘤患者机体均出现不同程度的免疫功能降低。目前,手术是治疗食管癌的主要方式,而手术给患者带来的疼痛对机体可产生免疫抑制,促进疾病进展[5]。因此,在手术过程中选择有效的麻醉方式,缓解机体免疫抑制的产生对手术的效果具有重要意义。临床研究显示[6],氟比洛芬酯在临床手术过程中的镇痛效果较好,得到临床广泛的应用。但目前关于氟比洛芬酯在手术麻醉过程中对机体免疫功能影响的报道相对较少。因此,本研究探究氟比洛芬酯对食管癌患者围术期外周血淋巴细胞亚群的影响。

1 资料与方法

1.1 研究对象

选择 2014 年 6 月 ~2016 年 8 月期间在我院择期行食管癌根治术患者为研究对象。纳入排除标准:(1)所有患者均经病理组织检查确诊为食管癌;(2)纳入研究前,所有患者均未接受抗肿瘤治疗;(3)所有患者均不存在手术禁忌症及药物过敏情况;(4)排除存在免疫系统疾病、妊娠期妇女及其他恶性肿瘤者;(5)所有患者及家属均知情同意,经纳入排除标准共收集食管癌患者 72 例,其中男 39 例,女 33 例;年龄 43~72 岁,平均年龄(49.38± 6.35)岁;临床肿瘤 ASA 分级,I 级 42 例,II 级 30 例,采用随机数字法将其分为氟比洛芬酯组(39 例)和对照组(33 例),其中氟比洛芬酯组男 22 例,女 17 例;年龄 43~71 岁,平均年龄(49.12± 6.23)岁;临床肿瘤 ASA 分级,I 级 23,II 级 16 例;对照组中男 17 例,女 16 例;年龄 43~72 岁,平均年龄(49.56± 5.16)岁;临床肿瘤 ASA 分级,I 级 19,II 级 14 例两组患者间性别、年龄及疾病分级均不存在差异(P>0.05)。所有操作均经我院伦理委员会审查通过。

1.2 研究方法

两组患者术前 6h 均行常规禁水、禁食,术前均给以静脉滴注 4 μg/kg 芬太尼、1.5 mg/kg 丙泊酚、0.05 mg/kg 咪达唑仑及 0.1 mg/kg 维库溴氨行全身麻醉,并行器官插管进行机械通气。术中所有患者静脉均持续给予普鲁泊福 5 mg/(kg*h),间断注射维库溴氨和芬太尼维持麻醉。术后行静脉自控镇痛,对照组患者泵入 5 mg 托烷司琼与 20 μg/kg 芬太尼;氟比洛芬酯组患者给予氟比洛芬酯 2 mg/kg。

1.3 观察指标

1.3.1 疼痛 分别于术后 12 h、24 h 和 48 h 采用疼痛视觉模拟评分(VAS)[7]评价患者疼痛情况,让患者根据自身感觉疼痛在直尺上选择疼痛的刻度,其中刻度 0 表示无痛,刻度 10 分表示剧痛,刻度越大,其疼痛程度越大。

1.3.2 生化指标 两组研究对象在纳入研究分别在术前 1h、术后 24 h、术后 72 h 分别抽取患者肘静脉血 3 mL,并加入肝素抗凝处理后置于 -80℃ 冰箱待检。将收集样本分成四份 100 μL 样本,分别加人异硫氰酸荧光素 10 μL 标记 $CD3^+$ 与 $CD4^+$ 单克隆抗体(购于美国 Beckman Coulter 公司),加入藻红蛋白 10 μL 标记 $CD8^+$ 与 $CD56^+$ 单克隆抗体,并放置于 25℃ 避光环境 1 小时,进一步加入红细胞裂解液(购于美国 Beckman Coulter 公司)静置 10 分钟后后进行离心,取上层血清加入磷酸盐缓冲液 1 mL 后,用流式细胞仪(Epics-XL 型流式细胞仪,由美国 Beckman Coulter 公司生产)检测血清 T 细胞中 $CD3^+$、$CD4^+$、$CD8^+$ 及 $CD56^+$ 的百分比,并计算 $CD4^+/CD8^+$ 值。

1.4 统计学分析

应用 SAS 9.4 进行数据分析,计量资料用均数± 标准差($\bar{x}$± s)表示,两组定量资料间均数比较采用独立样本 t 检验,同组患者不同时间定量资料采用配对 t 检验,采用卡方检验对计数资料进行分析,检验水准 α=0.05。

2 结果

2.1 两组患者术后不同点 VAS 评分比较

两组患者术后不同时刻 VAS 评分比较,差异均无统计学意义(P>0.05),见表 1。

表 1 两组患者术后不同点 VAS 评分比较

Table 1 Comparison of postoperative VAS scores different points in two groups

Groups	n	12h	24h	48h
Flurbiprofen group	39	2.01± 0.46	1.89± 0.31	1.83± 0.23
Control group	33	2.10± 0.38	1.92± 0.23	1.81± 0.25

2.2 两组患者不同时刻 T 淋巴细胞亚群水平比较

术后 1 h、24 h 两组患者各项指标均不存在差异(P>0.05);术后 24 h 两组患者 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均显著降低(P<0.05),术后 72 h 两组患者 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平均升高,且氟比洛芬酯组患者恢复到术后 1 h 水平,而对照组患者均仍低于术后 1 h,且术后 72 h 氟比洛芬酯组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均高于对照组,差异均有统计学意义(P<0.05),而 $CD8^+$ 与 $CD56^+$ 比例在两组各个时点均没有变化(P>0.05),见表 2。

2.3 两组患者不良反应的发生情况

两组患者麻醉过程中均未发现严重恶心、呕吐、呼吸抑制及皮肤瘙痒等不良反应。

3 讨论

食管癌是严重影响人们健康的恶性肿瘤之一,在我国发病率居高不下,严重影响我国居民的健康。既往研究显示[7-8],肿瘤的发病、进展及转归与机体免疫系统功能存在相关,且患者机体免疫功能随疾病的进展逐渐降低。此外,手术过程中患者伴有创伤、失血、低体温、疼痛等均会对机体免疫系统产生抑制作用,不仅给患者带来更多的痛苦,且会增加患者术中感染的发生[9]。从肿瘤患者角度,机体免疫功能出现降低意味着患者术后微肿瘤存在高转移的风险[10]。因此,对于食管癌手术治疗过程

表 2 两组术后不同时点 T 淋巴细胞亚群水平比较

Table 2 Comparison of the levels of postoperative T lymphocyte subsets different points in two groups

Groups	Time	$CD3^+$(%)	$CD4^+$(%)	$CD8^+$(%)	$CD4^+/CD8^+$	$CD56^+$(%)
Flurbiprofen group (n=39)	1h	66.39± 6.84	42.13± 6.26	25.36± 6.45	2.01± 0.76	11.52± 5.49
	24h	45.89± 5.77*	31.51± 4.64*	26.34± 3.43	1.34± 0.51*	13.43± 6.14
	72h	65.23± 5.38#	42.38± 4.39#	26.01± 2.19	2.02± 0.37#	12.31± 5.38
Control group (n=33)	1h	66.99± 5.29	41.94± 5.65	25.01± 3.47	2.01± 0.65	11.61± 4.38
	24h	45.89± 4.77*	31.51± 4.64*	26.10± 3.23	1.34± 0.51*	13.43± 4.14
	72h	50.23± 4.39*	33.34± 2.37*	26.07± 2.11	1.46± 0.37*	12.33± 3.28

Note: Comapred wtih postoperative 1h, *P<0.05; compared with control group, #P<0.05.

中如何采取措施缓解患者机体的免疫抑制具有重要意义。临床报道[11,12],氟比洛芬酯在临床手术过程中的镇痛效果较好,其能够靶向性聚集与患者伤口及炎症部位,蓄积于损伤部位及炎性反应组织中被前列腺素细胞摄取,抑制前列腺素的生成,降低机体组织对伤害刺激的反应度,但关于其对机体免疫功能影响的报道较少,因此,本研究探究氟比洛芬酯对食管癌患者围术期外周血淋巴细胞亚群的影响。

本研究选择我院择期行食管癌根治术患者 72 例将其随机分组,两组患者性别、年龄及疾病程度等基本资料均不存差异,从而排除研究过程中混杂因素的影响,增加结果的可靠性。研究发现,两组患者在麻醉后 12h、24 h 及 48 h 时刻的疼痛评分不存在差异,说明氟比洛芬酯的镇痛效果能够达到阿片类药物的作用,其作用机理主要通过降低机体脊髓前列腺素的合成,降低外周伤害性刺激向中枢传人发挥镇痛作用[13,14]。此外,两组患者麻醉过程中均未出现严重不良反应。既往报道[15,16],机体免疫系统能够识别癌细胞表面抗原,激活效应细胞发挥免疫应答杀伤癌细胞,其中,机体 $CD3^+$ 水平反映细胞免疫功能,$CD4^+$ 能够辅助抵御、杀伤癌细胞,$CD8^+$ 反映免疫抑制强度,$CD56^+$ 阳性表达标志着癌症的进展。此外,$CD4^+/CD8^+$ 值的降低可一般反应患者病情进展,患者预后效果较差[17]。本研究中,两组患者术后 24 h 两组患者 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均显著降低,说明患者因手术创伤、疼痛、麻醉等应激作用,激活机体应激系统产生机体免疫抑制,与既往报道一致[18];而术后 72h 两组患者 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平均升高,与治疗 72 h 后患者疼痛缓解、精神压力降低,且麻醉效果消失相关。此外,术后 72h 比洛芬酯组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 水平恢复到术前水平,而对照组水平仍然低于手术前与氟比洛芬酯组,说明阿片类麻醉能够抑制机体免疫功能,且持续时间较长,而氟比洛芬酯对机体免疫机体的抑制作用相对较低,其机制与氟比洛芬酯能够抑制前列腺素生成,阻断应激反应轴其免疫保护作用[19,20]。

综上所述,食管癌患者在手术过程中均出现免疫抑制,氟比洛芬酯麻醉效果较好,且其能够保护机体免疫功能,促进手术患者免疫功能的恢复,具有重要的临床价值。

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