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芬太尼透皮贴剂对吗啡不耐受晚期癌痛患者疼痛介质水平及生存质量的影响*

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摘要 目的:探讨芬太尼透皮贴剂对吗啡不耐受晚期癌痛患者疼痛介质水平及生存质量的影响。方法:回顾性分析我院2016年12月~2017年12月收治的102例吗啡不耐受晚期癌痛患者为研究对象,按治疗方式不同分为对照组和研究组,每组51例。对照组予以氨酚羟考酮片治疗,研究组予以芬太尼透皮贴剂治疗。比较两组的镇痛疗效,治疗前后血清疼痛介质、视觉模拟评分(VAS)、生活质量水平的变化和不良反应的发生情况。结果:治疗后,研究组镇痛总有效率显著高于对照组(86.27% vs. 68.23%, $P<0.05$)。治疗后,两组血清P物质(SP)、前列腺素E₂(PGE₂)及VAS评分均较治疗前显著下降,且研究组以上指标均明显低于对照组,两组血清β-内啡肽(β-EP)均较治疗前明显上升,且研究组显著高于对照组($P<0.05$)。两组治疗后精神状况、心理状况、功能状况、生理状况及社会功能评分均较治疗前显著上升,且研究组以上指标均显著高于对照组($P<0.05$)。治疗后,研究组恶心呕吐、便秘、头晕嗜睡发生率低于对照组($P<0.05$)。结论:芬太尼透皮贴剂对吗啡不耐受晚期癌痛患者的镇痛效果确切,能够调节疼痛介质表达,提高患者的生存质量,是治疗晚期癌痛有效、安全的阿片类药物。

关键词: 吗啡;晚期癌痛;芬太尼透皮贴剂;疼痛介质;生存质量

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Influence of Fentanyl Transdermal Patch on the Levels of serum Pain Medium and Quality of Life in Late-stage Cancer Patients with Pain and Morphine Intolerance*

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ABSTRACT Objective: To explore the influence of fentanyl transdermal patch on the level and quality of pain in patients with morphine intolerance late cancer pain. **Methods:** Retrospective analysis 102 cases of advanced cancer pain who treated from December 2016 to December 2017 as research object, according to the different treatment methods, those patients was divided into control group and the research group, 51 cases in each group. control group was treated with aminophenol oxycodone tablets, and the research group treated with fentanyl transdermal patch. Then analgesic effects, changes of serum pain media, visual analog scale (VAS), quality of life before and after treatment, and adverse reactions in both group were compared. **Results:** After treatment, analgesia total effective rate in research group was significantly higher than control group (86.27% and 68.23%, $P<0.05$). After treatment, the serum substance P (SP), Prostaglandin E₂ (PGE₂) and VAS scores in both group were significantly decreased than before treatment, while the above indicators of the research group were significantly lower than the control group. β-endorphin (β-EP) in both groups was increased than before treatment, and the research group was significantly higher than the control group, there was a statistical difference ($P<0.05$). after treatment, mental status, psychological status, functional status, physiological status and social function scores in the both groups was all increased than before treatment, while the above indicators of the research group were significantly higher than the control group ($P<0.05$). After treatment, occurrence rate of nausea and vomiting, constipation and dizziness in research group was lower than control group ($P<0.05$). **Conclusion:** Analgesic effect of fentanyl transdermal patch on morphine in patients with morphine intolerance late cancer pain is accurate, it can regulate the expression of pain medium and improve the quality of life of patients, which may be an effective and safe opioid drug in the treatment of advanced cancer pain.

Key words: Morphine; Advanced cancer pain; Fentanyl transdermal patch; Pain media; Quality of life

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前言

癌痛是晚期癌症患者的常见并发症之一,主要是因肿瘤直接浸润所致,明显影响患者生存质量,临床治疗应综合考虑是否遗留后遗症、长期止痛、创伤性、副作用、操作方法等因素,药物治疗是其重要手段^[1,2]。阿片类药物是癌痛治疗的第三阶段,其中吗啡为中晚期癌痛患者的首选药,其镇痛性较强,大部分患者可经吗啡达到理想镇痛,但仍有少数患者因吗啡不耐受而镇痛不满^[3,4]。临床研究建议^[5,6]对此类患者可替换其他阿片类药物以增强疗效。芬太尼透皮贴剂作为一种经皮给药的镇痛药,具有操作简便、作用时间长、生物利用度高等特点,现已广泛开展于临床^[7],但目前仍缺乏对其作用机制的全面报道。相关研究显示多种疼痛介质能够参与机体疼痛,以P物质(SP)、前列腺素E₂(PGE₂)及β-内啡肽(β-EP)异常表达最明显,通过调节其水平可能有利于控制疼痛^[8,9]。本研究主要通过探讨芬太尼透皮贴剂对吗啡不耐受晚期癌痛患者疼痛介质水平及生存质量的影响,旨在为癌痛的临床治疗提供参考依据。

1 资料与方法

1.1 一般资料

回顾性分析我院2016年12月~2017年12月收治的102例吗啡不耐受晚期癌痛患者为研究对象,纳入标准:符合吗啡不耐受诊断标准^[10];①长期疼痛、连续口服吗啡超过7天;②短期内吗啡剂量快速增加或者副反应增加;③副反应无法耐受,减小剂量后出现中重度疼痛;④疼痛改善不明显,加大剂量或者加用其他镇痛药物后仍不理想;⑤加大吗啡剂量后出现过无法耐受的副作用;⑥不良反应经对症处理后,仍持续增加或者存在;⑦疼痛和恶性肿瘤直接相关、且为中、重度;⑧接受过规范化三阶段止痛治疗;⑨观察期间未予以抗肿瘤治疗。排除标准:预计生存期低于1个月;明显呼吸困难;精神系统病变;急性爆发性疼痛为主;含本研究药物禁忌症;心肝肾等功能严重异常;哺乳或者妊娠阶段。

按治疗方式不同将所有患者随机分为对照组和研究组,每组51例。对照组年龄39~72岁,平均(61.49±8.51)岁;男22例,女29例;肿瘤类型:乳腺癌13例,食管癌10例,肺癌9例,胃癌12例,其他7例。疼痛类型:神经痛8例,内脏痛22例,躯体痛21例。研究组年龄38~74岁,平均(62.18±7.05)岁;男24例,女27例;肿瘤类型:乳腺癌11例,食管癌12例,肺癌10

例,胃癌13例,其他5例。疼痛类型:神经痛10例,内脏痛24例,躯体痛17例。两组一般临床资料如年龄、性别分布、原发疾病构成等比较差异均无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

102例患者按口服吗啡剂量作为参考基数换算相应药物剂量,芬太尼贴25尼贴考基数口服吗啡30mg/24h,对照组予以氨酚羟考酮片(规格:5mg/片,批号:160714, Mallinckrodt Inc)治疗,每6h一片。研究组予以芬太尼透皮贴剂(规格:4.2mg/贴,批号:150514,西安杨森制药有限公司)治疗,将其贴于无毛发的干燥区,确保和皮肤紧密接触,间隔3天更换1次,避免于同一部位重复贴敷。两组均持续治疗10d,期间患者均不使用其他镇痛药,于治疗结束时评估镇痛疗效,记录不良反应的发生情况。

1.3 观察指标

1.3.1 视觉模拟评分(VAS) 总分为10分,分数越高提示疼痛程度越明显^[10]。

1.3.2 镇痛疗效 疼痛全部消失为完全缓解;VAS降低在75%左右为明显缓解;VAS降低在50%左右为中度缓解;VAS降低在25%左右为轻度缓解,疼痛未减轻为未缓解。完全缓解、明显缓解及中度缓解为总有效^[10]。

1.3.3 疼痛介质测定 于治疗前及治疗结束时采集患者2mL空腹外周静脉血,以血液分离机按3000转/分钟分离10分钟,保存于-80℃低温箱中待检。用酶联免疫法测定SP、PGE₂、β-EB水平,试剂盒来自BD公司。

1.3.4 生活质量 用生活质量判定量表(GQOLI-74)进行评估,包含精神状况、心理状况、功能状况、生理状况及社会功能5个方面,分数越高提示生活质量越好^[11]。

1.4 统计学分析

数据处理选用SPSS18.0软件进行,计量资料用($\bar{x} \pm s$)表示,组间比较选用独立样本t检验进行,计数资料用[(例)%]表示,组间比较用 χ^2 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组镇痛效果的比较

治疗后,研究组镇痛总有效率为86.27%,显著高于对照组(68.83%),差异有统计学意义($P<0.05$),见表1。

表1 两组镇痛效果的比较[例(%)]

Table 1 Comparison of analgesic effect between two groups[n(%)]

Groups	n	Complete relief	Clearly relieved	Moderate relief	Mild relief	Not relieved	Total effective rate
Control group	51	3(5.88)	18(35.29)	14(27.45)	13(25.49)	3(5.88)	35(68.63)
Research group	51	6(11.76)	27(52.94)	11(21.57)	6(11.76)	1(1.96)	44(86.27) ^a

Note: Compared with the control group ^a $P<0.05$.

2.2 两组治疗前后血清疼痛介质水平及疼痛评分的比较

治疗前,两组血清SP、PGE₂、β-EB水平及疼痛评分比较差异无统计学意义($P>0.05$);治疗后,两组血清SP、PGE₂水平及VAS评分均较治疗前显著下降,且研究组以上指标均明显低

于对照组,两组血清β-EB水平均较治疗前明显增加,且研究组显著高于对照组,差异有统计学意义($P<0.05$),见表2。

2.3 两组治疗前后生存质量的比较

治疗前,两组生存质量评分比较差异无统计学意义($P>0.05$);

治疗后,两组生存质量评分均较治疗前明显上升,且研究组显著高于对照组,组间比较差异有统计学意义($P<0.05$),见表3。

表2 两组治疗前后血清疼痛介质水平及疼痛评分的比较($\bar{x} \pm s$)Table 2 Comparison of the serum pain medium levels and pain score between two groups before and after the treatment($\bar{x} \pm s$)

Groups	n	SP(mg/L)		PGE2(ng/L)		β -EB(ng/L)		VAS(Scores)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	51	571.40 $\pm$ 53.29	311.87 $\pm$ 42.06 ^b	265.69 $\pm$ 35.27	188.33 $\pm$ 23.46 ^b	104.61 $\pm$ 10.45	168.35 $\pm$ 20.84 ^b	6.54 $\pm$ 0.79	4.18 $\pm$ 0.58 ^b
		561.32 $\pm$ 58.41	241.09 $\pm$ 32.10 ^{ab}	271.20 $\pm$ 32.99	142.84 $\pm$ 18.75 ^{ab}	100.20 $\pm$ 12.65	191.52 $\pm$ 25.09 ^{ab}	6.27 $\pm$ 0.85	3.69 $\pm$ 0.45 ^a

Note: Compared with the control group ^a $P<0.05$; Compared with before treatment ^b $P<0.05$.

表3 两组治疗前后生存质量的比较($\bar{x} \pm s$,分)Table 3 Comparison of the quality of Life between two groups before and after the treatment($\bar{x} \pm s$, points)

Groups	n	Mental condition		Psychological condition		Functional status		Physiological condition		Social function	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	51	51.40 $\pm$ 7.11	66.38 $\pm$ 9.42 ^b	57.31 $\pm$ 6.50	70.08 $\pm$ 8.65 ^b	56.89 $\pm$ 8.44	67.31 $\pm$ 10.39 ^b	50.17 $\pm$ 7.51	62.80 $\pm$ 8.62 ^b	53.91 $\pm$ 8.71	64.09 $\pm$ 9.45 ^b
		53.16 $\pm$ 5.93	76.43 $\pm$ 11.81 ^{ab}	55.20 $\pm$ 8.46	76.54 $\pm$ 10.70 ^{ab}	58.01 $\pm$ 6.08	76.33 $\pm$ 9.43 ^{ab}	51.52 $\pm$ 6.40	78.60 $\pm$ 10.64 ^{ab}	55.08 $\pm$ 7.65	75.32 $\pm$ 12.18 ^{ab}

Note: Compared with control group ^a $P<0.05$; Compared with before treatment ^b $P<0.05$.

2.4 两组治疗前后不良反应发生情况的比较

治疗前,两组不良反应发生情况比较差异无统计学意义

($P>0.05$);治疗后,研究组恶心呕吐、便秘、头晕嗜睡发生率显

著低于对照组,差异有统计学意义($P<0.05$),见表4。

表4 两组治疗前后不良反应发生情况的比较[例(%)]

Table 4 Comparison of the incidence of adverse reactions between two groups[n(%)]

Groups	n	Nausea and vomiting		Constipation		Drowsiness	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	51	28(54.90)	16(31.37) ^b	24(47.06)	14(27.45) ^b	10(19.61)	8(15.69)
Research group	51	25(49.02)	7(13.73) ^{ab}	22(43.14)	6(11.76) ^{ab}	9(17.65)	2(3.92) ^{ab}

Note: Compared with control group ^a $P<0.05$; Compared with before treatment ^b $P<0.05$.

3 讨论

疼痛是晚期恶性肿瘤最自觉症状之一,呈持续加重的过程,长期过度剧烈的疼痛会对机体造成伤害性刺激,且可影响患者抗肿瘤治疗疗效,甚至缩短其远期生存率^[12,13]。止痛治疗是晚期癌痛患者的主要治疗手段,通过调节中枢神经系统对伤害性刺激感受,抑制神经传导通路,影响伤害性刺激的传导,起到止痛目的^[14,15]。药物治疗是目前癌痛治疗的重要方式,吗啡为第三阶梯止痛治疗的代表药物,其主要作用于 μ 受体,能够引起细胞膜超极化,导致神经元兴奋性下降,减少神经元末梢神经递质的分泌,抑制神经冲动传递,发挥镇痛作用^[16,17]。同时,吗啡能够作用于海马神经元,增加兴奋突触后电流,抑制其参与痛觉信号传导^[18]。但吗啡的长期应用可导致药物剂量加大、副作用加重及镇痛效果减弱等现象。

临床对于吗啡不耐受的晚期癌痛者可替换为其他阿片类药物,氨酚羟考酮片属阿片样激动剂,其生物利用度较高,具有

较强的镇静、镇痛效应,现已广泛应用于临床,作用机制和吗啡类似,但单一药物的局限性较大,小剂量应用的作用欠佳^[19]。且有研究显示^[20]氨酚羟考酮片对吗啡不耐受癌痛患者的镇痛效果欠佳。芬太尼作为一种阿片受体的激动剂,具有镇静及止痛作用,其止痛效应强于吗啡,有着较高的清除率,但其短效特效是慢性疼痛控制的缺陷。基于其脂溶性高、分子量小等特性,临床通过控释透皮治疗系统可以恒定速率维持血浆内芬太尼浓度^[21]。芬太尼透皮贴剂经皮肤缓慢给药,不容易出现成瘾性,是癌痛无创治疗的新方式。本研究结果显示芬太尼透皮贴剂组总有效率高于对照组,说明其在吗啡不耐受晚期癌痛患者的镇痛上有明显优势,可行性高。为明确其镇痛疗效,本研究进一步分析患者治疗前后血清疼痛介质水平的改变。

晚期恶性肿瘤因侵犯感觉神经、组织压迫,可诱导癌细胞分泌系列细胞因子,刺激痛觉过敏肽的过表达,导致局部微环境出现改变^[22]。SP是传递特疼痛的主要介质,可广泛分布于初级神经纤维组织内,神经产生刺激后可促进外周端及中枢端末

稍分泌 SP,并结合相应受体起到生理作用^[23]。同时,SP 能够诱导谷氨酸的分泌,调节痛觉传递,且可扩张血管,增加通透性。肿瘤细胞与相关免疫细胞还可释放内皮素、PGE2 等炎症趋化因子,增强伤害感受器的敏感性,且可提高组织对缓激肽、组织胺等刺激因子的敏感性,导致机体中枢痛觉敏化^[24]。 β -EP 作为一种阿片肽神经递质,多来源于肾上腺、垂体、丘脑等组织,能够调节伤害性感受器,镇痛作用较强,可抑制疼痛传递,避免 SP 释放,其活性不足时可诱导 SP 分泌,加剧疼痛^[25]。本结果显示两组治疗后血清 SP、PGE2 水平均降低, β -EP 明显上升,但芬太尼透皮贴剂组变化更明显,提示其可通过调节疼痛介质的表达,减轻机体疼痛,进一步分析显示芬太尼透皮贴剂治疗后 VAS 低于对照组,证实其镇痛效果。晚期癌痛能够明显影响患者心情、睡眠及活动,随着医学模式的转变及健康新理念的引进,生存质量已成为评估疗效的主要指标之一,为临床方案的选择提供依据^[26]。本研究结果显示芬太尼透皮贴剂治疗的患者生存质量的改善更明显,可能与芬太尼干预 μ 受体后能够增强痛阈,起到良好的镇痛作用,从而减轻患者因疼痛所致的焦虑、紧张等负面情绪有关。临床报道^[27]阿片类药物的毒性反应有较大的个体差异,容易受到药代动力学、亲和力及受体选择性等影响^[28]。本研究结果显示恶心呕吐及便秘是啡啡的主要不良反应,其次为头晕嗜睡及瘙痒,治疗后芬太尼透皮贴剂组不良反应发生率相对较低,可能和氨酚羟考酮片相比,芬太尼未经胃肠道吸收,因此其发生便秘及恶心呕吐可能性较低。但本研究观察时间较短,样本数较少,结果可能有一定偏差,有待更多前瞻、多中心研究。

综上所述,芬太尼透皮贴剂对啡啡不耐受晚期癌痛患者的镇痛效果确切,能够调节疼痛介质表达,提高患者的生存质量,是治疗晚期癌痛有效、安全的阿片类药物。

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未病先防"及"已病防变"两个层面,而膏方可在疾病尚未发生、发展之前介入调理,通过扶助人体正气,以避免"虚邪贼风"入侵;或在疾病早期,病位尚浅、病情尚轻、正气尚足的情况下,通过调理脏腑平衡,来预防疾病进一步发展,波及多个脏腑;亦可在瘥后扶正祛邪,增强免疫力,以防疾病复发等。

综上所述,益气安神膏临床疗效明显,服用方便,药力缓和而持久,可适用于临床慢性失眠患者的调理。恩师临证多年致力于膏方治未病的临床应用,其中应用益气安神膏治疗心脾两虚型失眠颇有成效,但我们因为时间、精力、资金等条件不足,受试对象地域性较为局限,纳入样本量较少,且因膏方剂型难以模仿故未设置双盲,加之我们对相关领域认识尚浅,故仍有待日后条件成熟再进行大样本、多中心、随机对照、双盲试验。

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