doi: 10.13241/j.cnki.pmb.2019.19.030

复方苦参注射液联合盐酸羟考酮缓释片治疗卵巢癌患者癌痛的临床研究 *

齐凤丽[1] 房 芹[2] 李明军[1] 高艳琨[1] 牛献谊[1] 于佳丽[3]

（1 内蒙古赤峰学院附属医院妇科 内蒙古 赤峰 024000；2 内蒙古赤峰学院附属医院肿瘤内科 内蒙古 赤峰 024000；
3 赤峰市医院妇科 内蒙古 赤峰 024000）

摘要 目的：探讨盐酸羟考酮缓释片联合复方苦参注射液对卵巢癌患者癌痛的影响。**方法：**选择我院 2015 年 1 月至 2018 年 6 月收治的 77 例卵巢癌患者，随机分为观察组(39 例)及对照组(38 例)。对照组给予羟考酮缓释片，观察组在对照组基础上加用复方苦参注射液，对比两组治疗前和治疗 1 个疗程后的疼痛数字评分(Numerical rating scale，NRS)评分和生活质量评分的变化，治疗期间每人每天的羟考酮用量及不良反应的发生情况。**结果：**治疗后，两组 NRS 评分均较治疗前明显下降，且观察组 NRS 评分明显低于对照组(P<0.05)。治疗后，观察组的疲乏、恶心呕吐、疼痛、食欲丧失、便秘评分明显低于对照组(P<0.05)。观察组每人每天羟考酮的用量、便秘及不良反应总发生率明显低于对照组(P<0.05)。**结论：**复方苦参注射液联合羟考酮可有效缓解卵巢癌的癌痛，降低羟考酮毒副作用，提高患者的生活质量。

关键词：盐酸羟考酮缓释片；复方苦参注射液；卵巢癌；癌痛；生活质量

中图分类号：R737.31 **文献标识码：**A **文章编号：**1673-6273(2019)19-3730-04

A Clinical Study on Compound Kushen Injection Combined with Hydroxycodone Hydrochloride Sustained Release Tablet in the Treatment of Ovarian Cancer Patients with Cancer Pain*

QI Feng-li[1], FANG Qin[2], LI Ming-jun[1], GAO Yan-kun[1], NIU Xian-yi[1], YU Jia-li[3]

(1 Gynecology Department, Affiliated Hospital of Chifeng University, Chifeng, Inner Mongolia, 024000, China;
2 Medical Oncology, Affiliated Hospital of Chifeng University, Chifeng, Inner Mongolia, 024000, China;
3 Gynecology Department, Chifeng Municipal Hoapital, Chifeng, Inner Mongolia, 024000, China)

ABSTRACT Objective: To investigate the effect of hydroxycodone hydrochloride sustained release tablet combined with compound kushen injection on the cancer pain in patients with ovarian cance. **Methods:** 77 cases of patients with ovarian cancer from Jan. 2015 to June 2018 in our hospital were chosen and randomly divided into the observation group (39 cases) and the control group(38 cases). The control group was given hydroxycodone hydrochloride sustained release tablet, the observation group was given compound kushen injection on the basis of the control group. The changes of NRS score and quality of life before and after 1 course of treatment, the amount of oxycodone per person per day and the occurrence of adverse reactions during the treatment were compared between two groups. **Results:** After treatment, the NRS scores of both groups were significantly lower than those before treatment, and the NRS score of observation group was significantly lower than that of the control group (P<0.05). After treatment, the scores of fatigue, nausea and vomiting, pain, loss of appetite and constipation in the observation group were significantly lower than those in the control group (P<0.05). The daily dose of oxycodone, constipation and total incidence of adverse reactions in the observation group were significantly lower than those in the control group (P<0.05). **Conclusion:** Compound Kushen injection combined with oxycodone could effectively alleviate the cancer pain of ovarian cancer, reduce the side effects of oxycodone and improve the patients' quality of life.

Key words: Oxycodone hydrochloride sustained-release tablets; Compound Kushen injection; Ovarian cancer; Cancer pain; Life quality

Chinese Library Classification(CLC): R737.31 Document code: A

Article ID: 1673-6273(2019)19-3730-04

前言

全世界每年约有 1000 万的新发癌症患者，其中 30%~50%的患者确诊时已经出现了中、重度疼痛[1-3]。卵巢癌的发病较为隐匿，70%的患者确诊时已经处于晚期，约有 75%~95%晚期患者存在癌痛症状[4-6]。疼痛会对卵巢癌患者的生活质量造成严重

* 基金项目：内蒙古自治区自然科学基金项目(2017MS0868)

作者简介：齐凤丽(1979-)，女，硕士，副主任医师，研究方向：妇科良恶性肿瘤，电话：13704764515，E-mail：Qifengli_221@163.com

(收稿日期：2019-01-30 接受日期：2019-02-26)

影响,如何缓解癌痛是卵巢癌防治的重点之一[7]。

按阶梯治疗原则,轻度癌痛者需采用吲哚美辛、阿司匹林等非甾体类镇痛药,中度癌痛需采用右旋丙氧芬、可待因等弱阿片类药物,重度癌痛者需采用羟考酮、吗啡、芬太尼等强阿片类药物[8,9]。患者长期服用镇痛药会出现一定程度的不良反应,如恶心、呕吐、便秘等,很多患者甚至在服用药物后会出现成瘾的情况[10-12]。因此,急需寻找副作用小、安全有效的癌痛治疗方法。本研究主要分析了盐酸羟考酮缓释片联合复方苦参注射液对卵巢癌患者癌痛及生活质量的影响,以期为卵巢癌患者的癌痛治疗提供参考依据。

1 资料与方法

1.1 一般资料

选择我院 2015 年 1 月至 2018 年 6 月收治的 77 例卵巢癌患者,均经组织病理学诊断为卵巢癌,且伴有癌性疼痛,预计生存期超过 3 个月,年龄为 18~79 岁;排除有精神病史者、智力障碍者、不能合作评价疼痛、生活质量者,有严重心、肝、肾功能障碍者,有阿片类药物滥用者,有明显呼吸抑制者;妊娠期、哺乳期妇女者。其中依从性较差或未能接受规定治疗者、观察期间自然失访、脱离者。77 例患者的平均年龄为 61.9± 5.8 岁,中度疼痛者 41 例,重度疼痛者 36 例。将 77 例患者随机分为观察组(39 例)及对照组(38 例),两组一般资料具有可比性。本研究所有患者知情同意,且经医院伦理委员会批准同意。

1.2 治疗方法

对照组患者给予盐酸羟考酮缓释片,中度疼痛者首次剂量为 10 mg,重度疼痛者首次剂量为 20 mg,中、重度疼痛者均为 12 h 口服一次药物; 并根据患者初次服药后的数字疼痛(NRS)评分进行剂量增加,NRS 1~3 分者增量为 25%,4~6 分者增量为 25%~50%,7~10 分增量为 50%~100%。若患者出现爆发痛,采用即释吗啡。

观察组在对照组基础上加用复方苦参注射液,将 15 mL 的复方苦参注射液加入到 250 mL 生理盐水中,进行静脉点滴,每日一次。

两组疗程均为 15 天,两组治疗期间均给予对症支持治疗,且未行其他止痛治疗。

1.3 观察指标

(1) 两组治疗前和治疗 1 个疗程后的 NRS 评分, 分值为 0~10 分,评分越高,患者癌痛越严重;(2)两组治疗前和治疗 1 个疗程后的生活质量评分, 采用生活质量调查问卷中的 QLQ-C30 量表进行评定,该量表总共有 30 个条目,5 个功能维度,6 个单一维度,3 个症状维度。其中整体生活质量表及 5 个功能维度评分越高,患者功能状态越好,生活质量越好;6 个单一维度及 3 个症状维度得分越高,症状越严重,生活质量越差;(3)两组每人每天羟考酮缓释片的平均用量;(4)治疗期间不良反应的发生情况。

1.4 统计学方法

采用 SPSS18.0 统计学软件进行数据处理, 计数资料和计量资料比较分别采用 x^2 或 t 检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 两组治疗前后 NRS 评分的对比

治疗后, 两组 NRS 评分均较治疗前明显下降, 且观察组 NRS 评分明显低于对照组($P<0.05$)。

表 1 两组治疗前和治疗 1 个疗程后的 NRS 评分对比(分)

Table 1 Comparison of the NRS score between two groups before and after one course of treatment(score)

Groups	n	Before treatment	After treatment	t	*P*
Observation group	39	5.3± 1.4	1.8± 0.4	21.857	<0.001
Control group	38	5.2± 1.5	4.3± 1.2	18.493	<0.001
t	-	0.303	-12.328	-	-
P	-	0.763	<0.001	-	-

2.2 两组治疗前后生活质量评分的对比

治疗前,两组的功能维度、症状维度、单一维度、整体生活质量对比差异无统计学意义($P>0.05$);治疗后,观察组的躯体功能明显高于治疗前,疲乏、疼痛、失眠、食欲丧失评分明显低于治疗前($P<0.05$);对照组的躯体功能、便秘评分明显高于治疗前,疲乏、恶心呕吐、疼痛、失眠明显低于治疗前($P<0.05$);观察组的疲乏、恶心呕吐、疼痛食欲丧失、便秘评分明显低于对照组($P<0.05$)。

2.3 两组羟考酮用量对比

观察组治疗期间每人每天羟考酮用量为 61.5± 5.9 mg,对照组用量为 101.4± 8.6 mg,观察组明显低于对照组($P<0.05$)。

2.4 两组治疗期间不良反应的发生情况对比

治疗期间,观察组便秘发生率明显低于对照组($P<0.05$),其不良反应总发生率明显低于对照组($P<0.05$)。

3 讨论

盐酸羟考酮是一种阿片类药物激动剂, 其采用缓释技术,患者服用后 38%的羟考酮会在早期快速释放, 在服用 1h 内迅速起效,而剩余 62%的羟考酮镇痛效果可持续 12h,具有较高的生物利用度,镇痛效果好,使用较为方便,为临床治疗中、重度癌痛的重要药物[13-16]。中药制剂用于恶性肿瘤治疗已有悠久的历史,在延长患者生存期、改善患者生活质量方面具有一定优势[17,18]。西药止痛虽然迅速、高效持久,但是副作用较大,中药制剂虽然起效缓慢,但副作用小,易于被患者接受。复方苦参注射液是由白土茯苓、苦参提取有效成分制成的中成药,具有扩张血管、抗肿瘤、改善微循环、提高机体免疫力、抑制中枢神经系统对疼痛反应的作用,可用于肿瘤癌痛的治疗[19-21]。

表 2 两组治疗前和治疗 1 个疗程后的生活质量评分对比(分)

Table 2 Comparison of the quality of life scores before and after one course of treatment between the two groups(score)

Index		Before treatment		After treatment	
		Observation group	Control group	Observation group	Control group
Functional dimension	Somatic function	55.2± 11.8	56.9± 12.4	63.3± 11.5*	62.8± 11.4*
	Role function	54.9± 15.3	55.9± 14.1	55.9± 10.8	56.1± 12.5
	cognitive function	65.9± 13.7	65.8± 13.1	65.3± 12.5	66.3± 13.2
	Emotional function	60.4± 12.5	58.6± 13.9	61.1± 14.1	59.8± 11.5
	social function	59.9± 11.5	60.9± 13.5	60.95± 13.4	60.5± 13.2
Symptom dimension	fatigue	55.4± 13.1	58.8± 13.1	40.1± 12.3*#	50.1± 12.9*
	Nausea and vomiting	21.9± 5.4	22.7± 5.9	22.1± 7.3	32.6± 9.8*
	pain	62.9± 12.8	63.8± 12.9	23.1± 5.8*#	32.9± 8.7*
Single dimension	expiratory dyspnea	13.2± 2.1	13.4± 3.8	13.1± 4.2	13.6± 3.8
	insomnia	56.8± 11.5	54.8± 14.1	41.8± 10.7*	42.1± 3.8*
	Loss of appetite	66.6± 12.5	67.2± 13.2	52.9± 11.5*#	66.8± 13.1
	astriction	26.5± 5.8	23.7± 4.5	25.9± 7.5#	46.9± 13.2*
	diarrhea	14.8± 2.8	15.4± 4.8	14.6± 3.5	14.8± 4.1
	economic sphere	57.9± 14.5	58.9± 11.5	58.6± 12.4	57.9± 11.4
Overall quality of life	-	49.6± 11.0	50.9± 12.9	50.8± 12.1	51.3± 13.2

Note: compared with before treatment, *P<0.05; compared with the control group, #P<0.05.

表 3 两组治疗期间不良反应发生情况的对比

Table 3 Comparison of the incidence of adverse reactions between the two groups during treatment

Groups	N	Astriction	Nausea and vomiting	Dizziness	Drowsiness	Dysuresia	Itch of skin	Total incidence rate
Observation group	39	11#	5	1	0	1	1	48.7(19/39)#
Control group	38	23	9	2	1	1	0	94.7(36/38)

Note: compared with the control group, #P<0.05.

本研究结果显示羟考酮联合复方苦参注射液可显著缓解卵巢癌患者的癌痛,且减少了羟考酮用量。主要是由于复方苦参注射液中具有多种有效镇痛成分,可通过多种非阿片类受体机制及阿片受体机制,如增加 γ- 氨基丁酸 α2 含量、减少炎症相关因子的合成及抑制离子型谷氨酸受体等,作用于患者的外周神经及中枢系统,从而达到止痛的作用。因此,二者联用时能减少阿片类药物的使用剂量,降低不良反应的发生[22-25]。此外,二者联合应用可更有效的改善卵巢癌癌痛患者的疲乏、疼痛、失眠、食欲丧失症状,主要是由于二者联合可更有效的缓解癌痛,而癌痛与乏力、失眠、食欲丧失密切相关,同时苦参可安五脏、养肝胆气、利九窍、定志益精、平胃气、令人嗜食,具有和胃止呕、提高患者食欲的作用[26-28]。治疗期间,观察组的便秘发生率明显降低,主要是由于复方苦参注射液中的苦参味苦、性寒,具有去湿、清火解毒之效,而白土茯苓性淡、甘、平,具有解毒消肿、清热利湿之效,苦参与白土茯苓共用,具有泻火解毒、清热利湿通便之效[29-31]。但本研究的样本量较少,数据可能存在一定偏倚,有待进一步增加样本量以明确。

综上所述,复方苦参注射液联合羟考酮可有效缓解卵巢癌的癌痛,减少羟考酮的毒副作用,提高患者生活质量。

参 考 文 献(References)

[1] Toyama K, Furuie H, Kuroda K, et al. Pharmacokinetic Bioequivalence Studies of an Extended-Release Oxycodone Hydrochloride Tablet in Healthy Japanese Subjects Under Fasting and Fed Conditions Without an Opioid Antagonist [J]. Drugs in R&D, 2017, 17(3): 363-370

[2] Inoue S, Saito Y, Tsuneto S, et al. A randomized, double-blind, non-inferiority study of hydromorphone hydrochloride immediate-release tablets versus oxycodone hydrochloride immediate-release powder for cancer pain: efficacy and safety in Japanese cancer patients[J]. Japanese Journal of Clinical Oncology, 2018, 48(6): 542-547

[3] Kibbe A H, Franko T S, Shah V M. Oxycodone hydrochloride immediate-release analgesic for managing severe pain: abuse-deterrent formulations [J]. Therapeutics and Clinical Risk Management, 2018, 14 (3): 779-782

[4] Xiang X, Yuan X, Lian Y, et al. Effect of oxycodone hydrochloride combined with flurbiprofen axetil for intravenous patient-controlled analgesia in lower abdominal patients [J]. Medicine, 2018, 97 (7): e9911

[5] Yamamoto M, Saito Y, Onodera Y , et al. Outcomes of an Independent

Clinical Study to Compare Branded and Generic Formulations of Sustained-Release Oxycodone [J]. Gan to Kagaku Ryoho, 2017, 44(3): 261-264

[6] Xie K, Zhang W, Fang W, et al. The analgesic efficacy of oxycodone hydrochloride versus fentanyl during outpatient artificial abortion operation: A randomized trial[J]. Medicine, 2017, 96(26): e7376

[7] Wang M, Wang M, Zhang Q, et al. Pharmacokinetics and Safety of Levetiracetam Extended-Release Tablets and Relative Bioavailability Compared with Immediate-Release Tablets in Healthy Chinese Subjects [J]. European Journal of Drug Metabolism & Pharmacokinetics, 2018(3): 1-9

[8] Scheidel B, Maritz M A, Gschwind Y J, et al. Bioavailability of oxycodone after administration of a new prolonged-release once-daily tablet formulation in healthy subjects, in comparison to an established twice-daily tablet [J]. International Journal of Clinical Pharmacology & Therapeutics, 2017, 55(11): 881-890

[9] Larance B, Dobbins T, Peacock A, et al. The effect of a potentially tamper-resistant oxycodone formulation on opioid use and harm: main findings of the National Opioid Medications Abuse Deterrence (NOMAD) study[J]. Lancet Psychiatry, 2018, 5(2): 155-166

[10] Mercadante S. Oxycodone extended release capsules for the treatment of chronic pain [J]. Expert Review of Neurotherapeutics, 2017, 17(5): 1

[11] Jobski K, Kollhorst B, Garbe E, et al. The Risk of Ischemic Cardio- and Cerebrovascular Events Associated with Oxycodone-Naloxone and Other Extended-Release High-Potency Opioids: A Nested Case-Control Study[J]. Drug Safety, 2017, 40(6): 1-11

[12] Haeseler G, Schaefers D, Prison N, et al. Combatting pain after orthopedic/trauma surgery- perioperative oral extended-release tapentadol vs. extended-release oxycodone/naloxone [J]. BMC Anesthesiology, 2017, 17(1): 91

[13] Ruan X, Chiravuri S, Kaye A D. FDA Approval of Extended-Release Oxycodone for Children with Severe Pain: A Step Forward [J]. Pain Medicine, 2016, 18(6): 1202-1203

[14] Gao L, Wang K X, Zhou Y Z, et al. Uncovering the anticancer mechanism of Compound Kushen Injection against HCC by integrating quantitative analysis, network analysis and experimental validation: [J]. Scientific Reports, 2018, 8(1): 624

[15] Zhang Y, Hui F, Yang Y, et al. Can Kushen injection combined with TACE improve therapeutic efficacy and safety in patients with advanced HCC? A systematic review and network meta-analysis[J]. Oncotarget, 2015, 8(63): 107258-107272

[16] Yoshimoto T, Ryu E, Tomiyasu S, et al. Efficacy and Safety of Oxycodone Injection for Relieving Cancer Pain: A Study in Japan Consisting of Two Open Trials for Intravenous and Subcutaneous Administration [J]. Biological & Pharmaceutical Bulletin, 2018, 41(6): 850-857

[17] Bhaisare M L, Khan M S, Pandey S, et al. Shape-oriented photodynamic therapy of cuprous oxide (Cu\r, 2\r, O) nanocrystals for cancer treatment[J]. RSC Adv. 2017, 7(38): 23607-23614

[18] Cui J H, Jiang W W, Liao Y J, et al. Effects of oxycodone on immune function in patients undergoing radical resection of rectal cancer under general anesthesia[J]. Medicine, 2017, 96(31): e7519

[19] Fu X, Zeng H, Guo J, et al. A PLGA-PEG-PLGA Thermosensitive Gel Enabling Sustained Delivery of Ropivacaine Hydrochloride for Postoperative Pain Relief [J]. Chemical & Pharmaceutical Bulletin, 2017, 65(3): 229-235

[20] Mihai M, Racovita S, Vasiliu A L, et al. Auto-template microcapsules of CaCO3/pectin and nonstoichiometric complexes as sustained tetracycline hydrochloride delivery carriers [J]. ACS Applied Materials & Interfaces, 2017, 9(42): 37264-37278

[21] Čalija B, Milić J, Janićijević J, et al. Ionically cross-linked chitosan-halloysite composite microparticles for sustained drug release [J]. Clay Minerals, 2017, 52(4): 413-426

[22] Moradiafrapoli F, Ebrahimi S N, Smiesko M, et al. HPLC-Based Activity Profiling for GABAA Receptor Modulators in Extracts: Validation of an Approach Utilizing a Larval Zebrafish Locomotor Assay[J]. Journal of Natural Products, 2017, 80(5): 1548-1557

[23] Odod A V, Nikonova E N, Nikonov S Y, et al. Electroluminescence of Zinc Complexes in Various OLED Structures [J]. Russian Physics Journal, 2017, 60(1): 7-13

[24] Attum B, Rodriguez-Buitrago A, Harrison N, et al. Opioid Prescribing Practices by Orthopaedic Trauma Surgeons After Isolated Femur Fractures[J]. Journal of Orthopaedic Trauma, 2018, 32(3): e106

[25] Cha S, Kim H K, Kho H S, et al. The Sustained Effects on Tear Volume of Pilocarpine Hydrochloride in Gelatin by Hydrogel Administered by An Implant-mediated Drug Delivery System[J]. Current Drug Delivery, 2017, 14(4): 581

[26] Matamala A M, Bertolotti M, Contini M P. Tramadol hydrochloride 75 mg/dexketoprofen 25 mg oral fixed-dose combination in moderate-to-severe acute pain sustained analgesic effect over a 56-h period in the postoperative setting[J]. Drugs of Today, 2017, 53(6): 339

[27] Kopecky E A, Vaughn B, Lagasse S, et al. Tolerability, Safety, and Effectiveness of Oxycodone DETERx in Elderly Patients ≥ 65?Years of Age with Chronic Low Back Pain: A Randomized Controlled Trial [J]. Drugs & Aging, 2017, 34(8): 603-613

[28] Zhu Y, Chen Y, Huang Z, et al. Unsuspected Metastatic Ovarian Cancer Revealed by 18F-NaF PET/CT Performed to Evaluate Lower-Back Pain[J]. Clinical Nuclear Medicine, 2017, 42(2): 154

[29] Jiang G, Balboni T, Taylor A, et al. Palliative Radiation Therapy for Recurrent Ovarian Cancer: Efficacy and Predictors of Clinical Response [J]. International Journal of Gynecological Cancer, 2017, 28(1): 1

[30] Lee K C, Lin H, Changchien C C, et al. Difficulty in diagnosis and different prognoses between colorectal cancer with ovarian metastasis and advanced ovarian cancer: An empirical study of different surgical adoptions[J]. Taiwanese Journal of Obstetrics and Gynecology, 2017, 56(1): 62-67

[31] Colombo N, Lorusso D, Scollo P. Impact of Recurrence of Ovarian Cancer on Quality of Life and Outlook for the Future[J]. International Journal of Gynecological Cancer, 2017, 27(6): 1134-1140