Supportive Care in Cancer (2019) 27:461–465
https://doi.org/10.1007/s00520-018-4313-z

ORIGINAL ARTICLE

The effect of a coix seed oil injection on cancer pain relief

Peirong Zhang[1] · Xiaoyan Meng[1] · Xiaohua Tang[1] · Li Ren[1] · Jun Liang[1]

Received: 27 February 2018 / Accepted: 6 June 2018 / Published online: 4 July 2018

Abstract

Background Pain is one of the most commonly reported symptoms in patients with advanced cancer, but is still less than optimally treated. The effect of traditional Chinese medicine in cancer pain treatment is nowadays getting more and more attention.

Objective To investigate the effect of a coix seed oil injection on cancer pain relief in a cancer center in a tertiary hospital in China.

Methods Patients in the treatment group received a coix seed oil injection for 2 weeks, while patients in the control group received equivalent 0.9% saline. The numeric rating scale was used to assess the pain level. The Quality of Life Questionnaire-Core 30 was used to assess life quality. The adverse drug reactions during the treatment process were observed.

Results Patients in the coix seed treatment group had significantly superior efficacy on pain control over those in the control group. Coix seed therapy significantly improved patients' scores reflecting by the Quality of Life Questionnaire-Core 30 (QLQ-C30) scale. In addition, the occurrence of adverse reactions such as constipation and nausea in the treatment group was significantly lower than that in the control group.

Conclusion The coix seed oil injection effectively reduced the pain level of cancer patients, significantly improved their life quality, and had no obvious adverse effects.

Keywords Coix seed oil · Cancer pain management · Numeric rating scale · Quality of life

Introduction

Pain is one of the most commonly reported symptoms in patients with advanced cancer and has been widely accepted to be considered as "the fifth vital sign" [3, 11, 18]. Studies have shown that 25% of patients with early-stage cancer suffer from cancer pain, while 60 to 80% of patients with advanced cancer suffer from cancer pain [15, 22]. Cancer pain not only results in physical discomfort, but also interferes with patients' life quality in terms of mentality, physiology, and society. Despite a lot of advances have been achieved in improving cancer pain management, many cancer patients are still less than optimally treated. With the number of cancer patients increasing year by year, the number of patients inflicted by cancer pain will rise markedly. Therefore, it is of great importance for clinical care givers to control cancer pain with their best efforts.

Coix lacryma-jobi, also called Job's tears, is a genus of Asian and Australian plants in the grass family. It is mainly planted in India, Japan, and China as a source of food, medicine, and ornamentation [24]. Coix seed and its active components have been reported to demonstrate many pharmacological effects, including anti-inflammatory, antioxidant activity, and anti-cancer activities [6, 20, 23]. As a traditional Chinese medicine, coix seed has been traditionally used for neuralgia, rheumatism, wart treatment, diuretic, promoting digestion, and inflammatory treatment [19]. Coix seed is now sometimes used in clinic to coordinate with chemotherapy [6, 8, 14]. However, few studies have investigated the effect of coix seed on cancer pain relief. Therefore, this study is aimed to evaluate its effect (Kanglaite injection, a coix seed oil extract) on relieving cancer pain in our oncology department.

Materials and methods

Study population

This study is ethically approved by the Human Research Ethics Committee of the Hospital and the Health Science

✉ Jun Liang
liangjunpku@126.com

[1] Department of Oncology, Peking University International Hospital, No. 1, Life Science Park Road, Beijing 102206, China

Center. All participants have signed the written informed consent. The inclusion criteria are as follows: diagnosed with advanced cancer by histopathology, with mild to severe pain, and ages more than 18 years old; mentally fully conscious and have good compliance; and with no history of psychosis, drug addiction, or anesthetics abuse. The exclusion criteria are as follows: presence of unconsciousness, severe cardiac, hepatic, or renal dysfunction (with alanine transaminase > 20 times of upper limit of normal, or creatinine clearance < 30 ml/min) and inability to understand the pain scale.

The sample size estimation of this study was calculated according to the data of a pilot study, setting a power of test as 0.9 and a significance level as 0.05. Ninety patients admitted to our oncology department from August 2015 to July 2016 and were included in this study, including 51 males and 39 females, with ages ranging from 34 to 78 years old. By using a random number table, patients were randomly divided into coix seed treatment group and control group; each contained 45 patients. The treatment group consisted of 25 males and 20 females, with average age of 61 years old, wherein 5 cases are mild pain (numeric rating scale (NRS) score 1–3), 26 are moderate pain (NRS score 4–6), and 14 are severe pain (NRS score 7–10). The control group consisted of 27 males and 18 females, with average age of 59 years old, wherein 4 cases are mild pain, 25 are moderate pain, and 16 are severe pain. The details of patients' demographic characteristics are listed in Table 1.

Treatment method

Patients in the coix seed treatment group received a coix seed oil injection (Kanglaite injection, Zhejiang Kanglaite Pharmaceutical Co., Ltd., China) 100 ml: 10 g, slowly intravenous drip, at a rate of approximately 2 ml/min, once daily, for 2 weeks. Patients in the control group received equivalent 0.9% normal saline. The main ingredient of Kanglaite injection is coix seed oil for injection, and the excipients are soybean phospholipids and glycerol for injection. Kanglaite injection is approved by the Chinese Food and Drug Administration (no. Z1097009) for its actions of anti-cancer and enhancing the therapeutic efficacy of radiotherapy and chemotherapy when combined with them. The possible mechanisms of action include inhibiting cancer cell proliferation, inducing apoptosis of cancer cells, downregulating genes such as cyclooxygenase-2 and matrix metalloproteinases, and inhibiting NF kappa B and protein kinase C signaling that has recognized importance in neoplasia [8, 21, 23]. Except for the main experimental interventions, patients in both groups received some supportive care medications. In the control group, patients with mild pain that had no impact on sleep were not given analgesics. Patients with moderate pain were given oral acetaminophen or weak opioids like codeine. Patients with severe pain were given strong opioids like morphine. For breakthrough pain, 10–20% of previous 24-h morphine dosage were given. In the treatment group, patients were not given routine analgesics. But if uncontrolled or intolerable pain occurred, morphine was used, which was seldom seen as the treatment progressed.

Outcome measurements

The effect of pain relief, the improvement on life quality, and adverse drug reactions were observed. All the data were obtained by independent trained nurses who were blinded to the study grouping.

- Assessment on pain control. Before treatment, NRS score was measured as a basic pain level. After 2-week treatment, the NRS score was measured again to assess the effect of pain control. The NRS score was measured by an independent nurse who was blinded to the study grouping.
- Assessment on life quality. The Quality of Life Questionnaire-Core 30 (QLQ-C30) from The European Organization for Research and Treatment of Cancer (EORTC) was used to assess life quality [17]. An independent nurse was trained to get familiar with the application of the questionnaire before the study started. When used, the questionnaire was translated into Chinese language. Before and after the treatment, patients were required to complete the questionnaire under the instruction of the trained nurse. Then, the questionnaires were collected and data were obtained. Higher score in functional domain and general health domain, or lower score in symptoms domain represents a higher quality of life.
- Adverse effects observation. After the treatment was started, two nurses were designated three times daily to observe the adverse effects including constipation, nausea, vomiting, dizziness, drowsiness, and dysuria. Also, patients were encouraged to report to the nurses if these adverse effects occurred. The episodes of adverse reactions occurring were documented.

Statistical analysis

GraphPad prism 6 was used for statistical analyses. The chi-square test was used for enumeration data comparison. The *t* test was used for measurement data comparison between two groups. For multiple comparisons, analysis of variance was used followed by Sidak's test. Differences were considered as statistically significant at $p < 0.05$.

Table 1 Demographic characteristics of participants

		Treatment ($n = 45$)	Control ($n = 45$)	Total ($n = 90$)	t (df), chi-sq, p value
Age (years)[a]		61.43 ± 16.41	59.32 ± 15.33	60.38 ± 17.76	t (88) = 0.6303, $p = 0.5301$
Gender[b]	Male	25	27	52	Chi-sq = 0.1822, $p = 0.6695$
	Female	20	18	38	
Primary tumor[b]	Lung/respiratory	8	6	14	Chi-sq = 4.361, $p = 0.7373$
	Gastrointestinal	6	9	15	
	Breast	4	7	11	
	Urogenital	10	5	15	
	Pancreas	5	6	11	
	Liver	4	6	10	
	Gynecological	5	3	8	
	Others	3	3	6	
Pain level[b]	Mild	5	4	9	Chi-sq = 0.2641, $p = 0.8763$
	Moderate	26	25	51	
	Severe	14	16	30	

[a] Mean and standard deviation

[b] Frequencies

Results

Efficacy of pain control

Before treatment, there were no differences in pain scores between coix seed group and control group (5.600 ± 0.3216 and 5.822 ± 0.3151, respectively, $p = 0.9823$). After treatment, pain scores in both groups were obviously decreased, but patients in the coix seed-treated group had more significantly decreased pain score as compared to those in control group (2.556 ± 0.3041 vs. 3.844 ± 0.3773, $p = 0.0257$) (Table 2).

Effect on life quality

Coix seed therapy significantly improved the patients' scores of all the five functional domains and general health domain and decreased the patients' scores of all the three symptom domains, whereas the control therapy only significantly decreased the patients' score of the pain domain, the other domains were not significantly changed. Importantly, after the coix seed treatment, the scores of functional domain and general health domain were markedly improved as compared to those after control treatment. In addition, the scores of three symptom domains in the coix seed treatment group were all markedly decreased as compared to those in the control treatment group.

In the five independent domains, coix seed therapy significantly decreased the scores of insomnia, inappetence, and diarrhea, but increased the score of constipation, whereas the score of financial difficulty was not significantly changed. The control therapy significantly decreased the score of inappetence and increased the score of constipation, whereas the scores of the other three domains were not significantly changed. The scores of insomnia, inappetence, constipation, and diarrhea in the coix seed treatment group were all significantly lower than those in the control treatment group (Table 3).

Occurrence of adverse reactions

Patients in the two groups both presented some common analgesic-related adverse reactions such as constipation, nausea, vomiting, dizziness, drowsiness, and dysuria. The occurrence rates of constipation and nausea in the coix seed treatment group were significantly lower than those in the control treatment group, whereas the occurrence rates of other adverse reactions in the two groups had no statistically significant difference (Table 4).

Table 2 Pain control in two groups before and after treatment

	Coix seed ($n = 45$)		Control ($n = 45$)	
	Before treatment	After treatment	Before treatment	After treatment
Pain score (means ± SD)	5.600 ± 0.3216	2.556 ± 0.3041[a,b]	5.822 ± 0.3151	3.844 ± 0.3773[a]

[a] $p < 0.05$ vs. "before treatment" in the same group

[b] $p < 0.05$ vs. "after treatment" in the control group

Table 3 Score of QLQ-C30 (V3.0) scale in the two groups

		Coix seed ($n = 45$)		Control ($n = 45$)	
		Before treatment	After treatment	Before treatment	After treatment
Functional domain	Physical function	65.53 ± 11.26	78.24 ± 11.86[a,b]	67.64 ± 12.58	71.25 ± 10.13
	Role function	62.74 ± 12.43	73.53 ± 12.64[a,b]	63.62 ± 13.65	68.62 ± 16.63
	Emotional function	58.12 ± 11.54	71.64 ± 13.28[a,b]	57.89 ± 9.42	62.28 ± 14.35
	Cognitive function	53.69 ± 10.96	68.72 ± 17.53[a,b]	55.95 ± 11.47	57.77 ± 15.48
	Social function	53.86 ± 9.97	67.79 ± 13.45[a,b]	52.71 ± 16.63	55.82 ± 16.67
General health domain		41.87 ± 18.63	67.43 ± 19.74[a,b]	41.36 ± 15.34	43.62 ± 14.62
Symptoms domain	Fatigue	41.76 ± 12.74	28.24 ± 11.76[a,b]	42.74 ± 11.17	39.60 ± 11.70
	Nausea/vomiting	35.76 ± 12.69	23.54 ± 11.31[a,b]	35.78 ± 14.34	32.44 ± 13.30
	Pain	95.42 ± 12.25	56.32 ± 14.49[a,b]	93.45 ± 13.34	68.53 ± 15.54[a]
Insomnia		42.46 ± 13.12	28.21 ± 12.11[a,b]	43.13 ± 15.31	37.28 ± 16.12
Inappetence		48.24 ± 12.26	36.89 ± 12.36[a,b]	46.40 ± 10.34	40.54 ± 13.32[a]
Constipation		31.67 ± 11.46	52.34 ± 14.20[a,b]	28.41 ± 11.23	62.64 ± 14.65[a]
Diarrhea		22.43 ± 12.45	16.54 ± 12.21[a,b]	20.48 ± 11.53	19.54 ± 10.36
Financial difficulty		38.16 ± 16.94	42.40 ± 16.58	36.86 ± 16.95	41.23 ± 17.92

[a] $p < 0.05$ vs. "before treatment" in the same group

[b] $p < 0.05$ vs. "after treatment" in the control group

Discussion

A good control of cancer pain has been considered as an essential problem in cancer rehabilitation and palliative treatment. Although pain relief for cancer patients is acknowledged to be a basic human right, the realities of cancer pain management are not satisfying, even in many developed countries [4]. In China, pain control for cancer patients is still waiting for further improvement. Some Chinese researchers reported that more than 52% of nurses regarded cancer pain as unavoidable and incurable, thus leaving patients to endure the pain as it should be. More than 64% of nurses had an obscure comprehension for cancer pain definition and sometimes distrusted cancer patients' complains about pain with varying degrees [13]. So, despite advances in cancer pain control, there still remain large gaps, especially in developing countries, to achieve the goal of painless sleep, painless rest, and painless activities for cancer patients.

The benefit from pain management interventions for cancer patients mainly reflected in pain control and life quality improvement. But while the analgesic effect of opioids is enhanced with the increase of dosage, so does the adverse reactions [10]. This is one of the reasons that the treatment effect of opioids on cancer pain relief is not desirable. Other treatment methods for cancer pain, such as biotherapy and surgery, more or less, have their limitations or intolerable adverse effects for cancer patients [12]. So, the traditional Chinese medicine, known for its good efficacy and few side effects in cancer pain treatment, is nowadays getting more and more attention [16].

Coix seed and its extract have been demonstrated to have many effects including anti-inflammatory, antioxidant, xanthine oxidase inhibitory, and anti-cancer activities [2, 24]. In our cancer center, Kanglaite (coix seed oil extract) injection is mainly used to coordinate with chemotherapy. We intended to investigate if Kanglaite also had a pain relief effect in cancer patients. In the present study, we evaluated the pain control effect of Kanglaite injection and found that it can significantly reduce the pain level and improve life quality of cancer patients, while the side effects were relatively few. Regarding the mechanism of action for analgesia with coix seed extract, little literatures have discussed before. But previous studies mentioned that coix seed significantly downregulated gene expressions of cyclooxygenase-2 and reduced the prostaglandin E2

Table 4 Occurrence of adverse reactions

Group	n	Constipation	Nausea	Vomiting	Dizziness	Drowsiness	Dysuria	Others
Treatment	45	22[a]	6[a]	4	5	3	4	2
Control	45	28	12	5	7	5	6	3

[a] $p < 0.05$ vs. control group

level in serum [7, 21], which are two substances strongly related to pain pathways [1, 5, 9]. Therefore, we speculated that the pain relief effect of coix seed in our study may be to a certain extent mediated by those two mechanisms. However, further studies are still needed to confirm this speculation and to elucidate the underlying mechanisms.

Conclusion

This study provided evidence that the coix seed oil injection effectively reduced the pain level of cancer patients suffering from mild to severe pain, significantly improved their life quality, and had no obvious adverse effects. But caution should be used in generalizing the results in other countries, because this paper is limited to a single-center study of advanced cancer patients in China.

Compliance with ethical standards

This study is ethically approved by the Human Research Ethics Committee of the Hospital and the Health Science Center. All participants have signed the written informed consent.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Bastos LC, Tonussi CR (2010) PGE(2)-induced lasting nociception to heat: evidences for a selective involvement of A-delta fibres in the hyperpathic component of hyperalgesia. Eur J Pain 14(2):113–119. https://doi.org/10.1016/j.ejpain.2009.04.002
2. Chen HJ, Lo YC, Chiang W (2012) Inhibitory effects of adlay bran (Coix lachryma-jobi L. var. ma-yuen Stapf) on chemical mediator release and cytokine production in rat basophilic leukemia cells. J Ethnopharmacol 141(1):119–127. https://doi.org/10.1016/j.jep.2012.02.009
3. Eaton LH, Meins AR, Mitchell PH, Voss J, Doorenbos AZ (2015) Evidence-based practice beliefs and behaviors of nurses providing cancer pain management: a mixed-methods approach. Oncol Nurs Forum 42(2):165–173. https://doi.org/10.1188/15.ONF.165-173
4. Fielding F, Sanford TM, Davis MP (2013) Achieving effective control in cancer pain: a review of current guidelines. Int J Palliat Nurs 19(12):584–591. https://doi.org/10.12968/ijpn.2013.19.12.584
5. Goswami SK, Inceoglu B, Yang J, Wan D, Kodani SD, da Silva CA, … Hammock BD (2015) Omeprazole increases the efficacy of a soluble epoxide hydrolase inhibitor in a PGE(2) induced pain model. Toxicol Appl Pharmacol 289(3):419–427. https://doi.org/10.1016/j.taap.2015.10.018
6. Huang HC, Hsieh WY, Niu YL, Chang TM (2014) Inhibitory effects of adlay extract on melanin production and cellular oxygen stress in B16F10 melanoma cells. Int J Mol Sci 15(9):16665–16679. https://doi.org/10.3390/ijms150916665
7. Hung WC, Chang HC (2003) Methanolic extract of adlay seed suppresses COX-2 expression of human lung cancer cells via inhibition of gene transcription. J Agric Food Chem 51(25):7333–7337. https://doi.org/10.1021/jf0340512
8. Lu X, Liu W, Wu J, Li M, Wang J, Wu J, Luo C (2013) A polysaccharide fraction of adlay seed (Coixlachryma-jobi L.) induces apoptosis in human non-small cell lung cancer A549 cells. Biochem Biophys Res Commun 430(2):846–851. https://doi.org/10.1016/j.bbrc.2012.11.058
9. Ma K, Zhou QH, Chen J, Du DP, Ji Y, Jiang W (2008) TTX-R Na+ current-reduction by celecoxib correlates with changes in PGE(2) and CGRP within rat DRG neurons during acute incisional pain. Brain Res 1209:57–64. https://doi.org/10.1016/j.brainres.2008.02.096
10. Palos GR (2008) Opioids and cancer survivors: issues in side-effect management. Oncol Nurs Forum 35(Suppl):13–19. https://doi.org/10.1188/08.ONF.S1.13-19
11. Phillips JL, Lovell M, Luckett T, Agar M, Green A, Davidson P (2015) Australian survey of current practice and guideline use in adult cancer pain assessment and management: the community nurse perspective. Collegian 22(1):33–41
12. Portenoy RK (2011) Treatment of cancer pain. Lancet 377(9784):2236–2247. https://doi.org/10.1016/S0140-6736(11)60236-5
13. Qiu X, Li X, Zhang D (2009) Investigation and nursing strategies for barriers in cancer pain control. Chin Nurs Res 23(10):867–869
14. Qu D, He J, Liu C, Zhou J, Chen Y (2014) Triterpene-loaded microemulsion using Coix lacryma-jobi seed extract as oil phase for enhanced antitumor efficacy: preparation and in vivo evaluation. Int J Nanomedicine 9:109–119. https://doi.org/10.2147/IJN.S54796
15. Schreiber JA (2014) Understanding the cancer pain experience. Curr Pain Headache Rep 18(8):440. https://doi.org/10.1007/s11916-014-0440-5
16. Smith ME, Bauer-Wu S (2012) Traditional Chinese medicine for cancer-related symptoms. Semin Oncol Nurs 28(1):64–74. https://doi.org/10.1016/j.soncn.2011.11.007
17. Snyder CF, Blackford AL, Okuyama T, Akechi T, Yamashita H, Toyama T, … Wu AW (2013) Using the EORTC-QLQ-C30 in clinical practice for patient management: identifying scores requiring a clinician's attention. Qual Life Res 22(10):2685–2691. https://doi.org/10.1007/s11136-013-0387-8
18. Thompson J (2014) Pain management in cancer nursing. Br J Nurs 23(10):S17. https://doi.org/10.12968/bjon.2014.23.Sup10.S17
19. Wang L, Chen J, Xie H, Ju X, Liu RH (2013) Phytochemical profiles and antioxidant activity of adlay varieties. J Agric Food Chem 61(21):5103–5113. https://doi.org/10.1021/jf400556s
20. Wang L, Sun J, Yi Q, Wang X, Ju X (2012) Protective effect of polyphenols extract of adlay (Coix lachryma-jobi L. var. ma-yuen Stapf) on hypercholesterolemia-induced oxidative stress in rats. Molecules 17(8):8886–8897. https://doi.org/10.3390/molecules17088886
21. Woo JH, Li D, Wilsbach K, Orita H, Coulter J, Tully E, … Gabrielson E (2007) Coix seed extract, a commonly used treatment for cancer in China, inhibits NFkappaB and protein kinase C signaling. Cancer Biol Ther 6(12):2005–2011
22. Yost KJ, Hahn EA, Zaslavsky AM, Ayanian JZ, West DW (2008) Predictors of health-related quality of life in patients with colorectal cancer. Health Qual Life Outcomes 6:66. https://doi.org/10.1186/1477-7525-6-66
23. Zhan YP, Huang XE, Cao J, Lu YY, Wu XY, Liu J, … Ye LH (2012) Clinical safety and efficacy of Kanglaite(R) (Coix seed oil) injection combined with chemotherapy in treating patients with gastric cancer. Asian Pac J Cancer Prev 13(10):5319–5321
24. Zhao M, Zhu D, Sun-Waterhouse D, Su G, Lin L, Wang X, Dong Y (2014) In vitro and in vivo studies on adlay-derived seed extracts: phenolic profiles, antioxidant activities, serum uric acid suppression, and xanthine oxidase inhibitory effects. J Agric Food Chem 62(31):7771–7778. https://doi.org/10.1021/jf501952e