Electroacupuncture Versus Analgesics for Patients with Stage IIIB Cervical Cancer Post Cisplatin Chemotherapy

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ABSTRACT

Background: The prevalence of pain at advanced cervical cancer stages is increasing. Existing World Health Organization recommendations for management comprises a 3-step ladder of analgesic therapy but this still cannot address this pain optimally. An alternative therapy used to reduce pain, acupuncture, is almost without side-effects, is safe, and is easy to implement. This study compared electroacupuncture (EA) versus paracetamol 500 mg +10-mg codeine therapy for patients with stage-IIIB cervical cancer post cisplatin chemotherapy.

Materials and Methods: Participants were divided into 2 groups (treatment and control groups). A quasi-experimental study was conducted using a nonequivalent control group pretest–post-test design. Participants in the treatment group were given EA for 30 minutes 10 times over 3 weeks, while participants in the control group were given paracetamol 3×500 mg and codeine 3×10 mg orally every day for 3 weeks. Statistical analysis used paired *t*-tests, a Wilcoxon test, an independent *t*-test, or a Mann–Whitney-*U* test with $P < 0.05$.

Results: Pretest and post-test pain-scale levels were 5.39 ± 0.62 and 4.57 ± 0.88 , respectively ($P < 0.001$). Average endorphin- β levels at pretest and post-test were 571.80 ± 281.13 and 491.14 ± 272.14 , respectively ($P = 0.818$). Median values of quality of life at pretest and post-test were 681.75 (range: 503.80–915.20) and 635.25 (range: 538.20–781.20; $P = 0.383$), respectively.

Conclusions: Pain-control therapy using drugs or EA produces similar results. However, EA, subjectively, produces improved pain-scale results better than pharmaceuticals.

Keywords: cancer pain, paracetamol–codeine, electroacupuncture, pain scale, β -endorphin, quality of life

INTRODUCTION

CERVICAL CANCER IS A SERIOUS KIND of malignancy in women. In developed countries, cervical cancer is the third-most gynecologic malignancy, while, in developing countries such as Indonesia, cervical cancer is the second-most-common gynecologic malignancy among all types of cancer in women.¹ Almost all patients with cancer suffer from pain. In patients with more-advanced cancer, more than 80% have moderate-to-severe pain, while 33% of chronic pain can still be felt by patients with cancer who have received complete therapy for cancer.²

Cancer-pain therapy can be conducted by administering antipain pharmaceuticals or by nonpharmacologic techniques according to the World Health Organization (WHO) stepladder analgesic protocol.

In this study, patients with stage-IIIB cervical cancer were examined post cisplatin chemotherapy. These patients had moderate pain scores and had received treatment with 500 mg of paracetamol +10 mg of codeine. This treatment was compared to electroacupuncture (EA). The study was conducted because data shows that 20%–40% of cancer pain is not resolved adequately despite patients being given therapy in accordance with the WHO stepladder analgesic

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protocol. There are several side-effects of paracetamol + codeine, such as constipation, urinary retention, nausea, sedation, respiratory depression, myoclonus, delirium, sexual dysfunction, and hyperalgesia.^{3,4}

Pain affects all aspects of a patient's quality of life (QoL) and ability to comply with treatment in an effort to restore health and/or achieve a peaceful terminal state or death.⁵ In developed countries, 50%–80% of cancer pain is not treated adequately, and 25% of all patients with cancer in the world die with severe unresolved cancer pain.⁶ Even when implementing the WHO pain-management guidelines, the resulting data showed that there were still ~40% of patients with untreated pain; thus, supporting therapy is needed to overcome this pain. Complementary medicine nonpharmacologic therapy is generally considered to be relatively safe and is often used as adjunctive therapy to other standard pain-management approaches.⁷

Nonpharmacologic techniques that have been developed to deal with cancer pain include acupuncture as a pain-relief option that is almost without side-effects, and is safe and easy to implement; it can reduce drug usage by as much as 80%. The analgesic effect of acupuncture has been recognized by the WHO and was licensed by the U.S. Food and Drug Administration in 1996. The mechanism of acupuncture can work at local, segmental, and central levels, namely, on the hypothalamic–pituitary pathway. This pathway becomes active due to needle insertions and results in endogenous opioid secretions that involve transmitting β -endorphins to blood vessels and cerebrospinal fluid.^{8,9}

β -endorphins work directly on pain pathways in the central nervous system (CNS) and spinal cord as neurotransmitters. This produces analgesia and homeostatic effects in several systems involved in healing processes, including the immune, cardiovascular, and respiratory systems. In addition, acupuncture is believed to reduce symptoms caused by cancer as well as reducing the side-effects of anticancer therapy; thus, acupuncture can improve a patient's quality of life.¹⁰ Over the past 20 years, there have been many studies on acupuncture for treating cancer pain but the results are inconsistent. Therefore, clinicians still have difficulty making decisions regarding whether or not to apply acupuncture therapy when treating patients who have cancer-related pain.¹¹

This study was conducted on patients who still felt pain even after receiving therapy per the WHO pain-management guidelines. The current authors explored the effects of acupuncture, particularly EA, on pain scores, plasma β -endorphin levels, and QoL in patients with stage-IIIB cervical cancer post cisplatin chemotherapy who still had moderate pain.

METHODS

Participants

Participants in this study were patients with stage-IIIB cervical cancer post cisplatin chemotherapy with pain levels

of 4–6 (on the Wong–Baker Faces pain-rating scale). Inclusion criteria were: cooperation during acupuncture therapy; stage-IIIB cervical cancer¹²; post 4 courses of cisplatin chemotherapy; pain level of 4–6 (Wong–Baker Faces pain-rating scale); and not using pain medication at least 1 week before the study. Participants also had to be receiving therapy according to WHO pain-management step-2 (moderate pain), namely, 500 mg of paracetamol +10 mg of codeine.

Exclusion criteria were: pain not caused by cervical cancer; pain due to surgery; receiving analgesic drugs for <1 week before the study; contraindications to receiving 500 mg of paracetamol +10 mg of codeine; and/or ever underwent radiation. In addition patients were excluded if they had contraindications to EA use, such as blood-clotting abnormalities, pacemaker installations, skin disorders, pregnancies, wounds/tumors in the puncture areas, and/or physical disabilities that prevented acupuncture therapy.

Design

This study used a nonequivalent control group, pretest–post-test design. The study was conducted from July to December 2019. There were 28 participants divided into 2 groups: a treatment group ($n=14$) and a control group ($n=14$; Fig. 1). Patients in the treatment group received EA therapy, while those in the control group received 500 mg of paracetamol +10 mg of codeine. Each group received therapy for 3 weeks. Participants' pain was recorded using the Wong–Baker Faces pain-rating scale.^{13,14} QoL was determined with the European Organization for Research and Treatment of Cancer Quality-of-Life-Questionnaire-Core-30 (EORTC-QLQ30) questionnaire. β -endorphin levels in blood plasma were also measured.

EA is performed at certain acupuncture points. Electrical stimulation with notification techniques is provided, using dense-disperse waves of an intensity that can be tolerated by a patient for 30 minutes with a combination frequency of 2/50 Hz. The needle is inserted perpendicularly to *Hegu* (LI 4), *Zusanli* (ST 36), *Sanyinjiao* (SP 6), and *Taichong* (LR 3) until the patient feels a sensation of rheumatic pain, stiffness, numbness, and/or tingling caused by the electric current provided at the needle-insertion site. First, needles are inserted at the acupuncture points on the right and left (bilateral) symmetrical parts of the body. Electrostimulator cables are then attached to the needles that have been inserted at all 4 points, with a frequency of 2/50 Hz continuous waves, for 30 minutes.

SP 6 is on the tibial side of the lower leg at the posterior part of the medial tibia. This point is located 3 *cun* (or 4 fingers) above the medial malleolus (3" above the top of the medial malleolus), posterior to the tibia with an 0.5–0 puncture depth, with a 9-*cun* direction of the needle toward the tibia. This point is used for abnormalities in gynecologic organs.

FIG. 1. The process of participant identification.

LI 4 is located on the human dorsum on the middle radial side of the second metacarpal bone (between metacarpal bones I and II), with a depth of 0.8–1.3 *cun* perpendicular. This point is the most-common point used for pain relief because the point produces the greatest analgesic effect on the body.

ST 36 is anterior on the leg at 3 *cun* or 4 fingers under the patella (under the “hole” when the knee is flexed), 1 *cun* lateral to the tibia crest as deep as 0.5–1.3 *cun* perpendicular. Stimulation at this point increases brain endomorphin.

LR3 is on the dorsal leg, between the 1st and 2nd metatarsal bones, at the distal curve of the 2 bones, next to the dorsalis pedis artery, with a depth of 0.5 *cun* perpendicular puncture. This point is often combined with LI 4 to relieve pain and Calm the Mind.

EA therapy was performed 10 times for 3 weeks. Meanwhile, the WHO stepladder analgesic protocol was

administered to participants in the control group at a dose of 500 mg of paracetamol and 10 mg of codeine, both 3 × daily for 3 weeks orally.

Ethics Approval

This study received ethics approval from the ethics committee of the Dr. Soetomo General Academic Hospital, in Surabaya, Indonesia, where the study was conducted, according to the Declaration of Helsinki (1450/KEPK/VIII/2019). Informed consent for publication was obtained from the patients.

QoL Measurements

The QoL in this study refers to health-related quality of life that illustrates the functional effects of the disease and

the results of therapy experienced by the patients. Data were obtained from interviews using a specific questionnaire for cancer, namely the Indonesian version of the EORTC QLQ-C30. The EORTC QLQ-C30 was declared to be valid and reliable with a Cronbach's α -value >0.70 .¹³

β -Endorphin Levels

Each participant's blood sample was taken before and after the WHO stepladder analgesic protocol or EA therapy. Blood plasma was stored in a cooler at -70°C until all samples were collected. These samples were as much as $\pm 3\text{ mL}$. The blood was stored in ethylenediamine tetra-acetic acid tubes with the anticoagulant cooled to $2^{\circ}\text{--}8^{\circ}\text{C}$ for at least 1 day prior. Then, the blood samples were delivered to the hospital's laboratory. The blood samples were centrifuged at $1000g$ for 15 minutes at 4°C to produce 1 cc of blood plasma. Then, endorphin hormone levels were tested. β -endorphin in plasma serum was identified using an enzyme-linked immunosorbent assay (MD Biosciences, Zürich, Switzerland).

Statistical Analysis

The data obtained were processed with the SPSS 21.0 program (IBM Corp., Armonk, NY, USA). Shapiro–Wilk test results were measured to determine the data distribution. The statistical tests used in this study included dependent paired t -tests, a Wilcoxon test, an independent t -test, or a Mann–Whitney- U test, with $P < 0.05$.

RESULTS

Characteristics of the Participants

There were no significant age differences between the 2 groups (treatment and control). Most participants in the treatment group were ages 36–45 (42.86%) and most participants in the control group were ages 46–55 (64.29%). Most participants were junior-high-school graduates (35.71%) in the treatment group and elementary-school graduates in the control group (35.71%). Most participants were housewives (64.29%) in each group (Table 1).

Pain-Scale Values

The average pretest and post-test pain-scale values of patients in the control group were 5.36 ± 0.63 and 5.14 ± 0.66 , respectively ($P = 0.405$). Meanwhile, the average pretest and post-test pain-scale values of patients in the treatment group were 5.43 ± 0.65 and 4.00 ± 0.68 , respectively ($P = 0.003$). Comparisons of the patients' pain-scale values are shown in Table 2. The average pain-scale values in the control group and the treatment group at pretest and post-test were 5.39 ± 0.62 and 4.57 ± 0.88 , respectively ($P < 0.001$).

TABLE 1. CHARACTERISTICS OF PARTICIPANTS

Variables	Group	
	Control (n = 14)	Treatment (n = 14)
Age	45.28 $\pm$ 12.62	52.50 $\pm$ 5.78
26–35	4 (28.57)	0 (0.00)
36–45	6 (42.86)	1 (7.14)
46–55	1 (7.14)	9 (64.29)
56–65	1 (7.14)	4 (28.57)
≥ 65	2 (14.28)	0 (0.00)
Education		
Not attending school	2 (14.28)	1 (7.14)
Elementary school	4 (28.57)	5 (35.71)
Junior high school	5 (35.71)	4 (28.57)
Senior high school	2 (14.28)	3 (21.43)
Undergraduate	1 (7.14)	1 (7.14)
Occupation		
Housewife	9 (64.29)	9 (64.29)
Public servant	1 (7.14)	3 (21.43)
Private-sector employee or entrepreneur	4 (28.57)	2 (14.28)

Numerical data was shown as mean $\pm$ standard deviation, while categorical data was shown as frequency (percentage).

QoL Values

The average pretest and post-test values of the EORTC QLQ-C30 in the control group and the treatment group were 702.60 ± 117.01 and 667.99 ± 83.13 , respectively. The control group and the treatment group value at the time of pretesting was $P = 0.869$ and post-testing was $P = 0.383$. The median values of QoL in the control group at pretest and post-test were 666.95 (range: 534.30–983.50) and 665.35 (range: 538.20–781.20), respectively. Meanwhile, the median values of QoL at pretest and post-test was 681.75 (range: 503.80–915.20) and 635.25 (range: 538.20–781.20), respectively. The average value of QoL in the control group

TABLE 2. COMPARISON OF ANALGESIC AND ELECTROACUPUNCTURE ADMINISTRATION FOR PATIENTS' PAIN

	Pretest	Post-test	P
Wong Baker pain scale			
Treatment	5 (5–6)	4 (3–5)	0.003*
Control	5 (4–6)	5 (4–6)	0.405
β -endorphin level			
Treatment	503.32 $\pm$ 220.01	460.50 $\pm$ 227.87	0.221
Control	640.27 $\pm$ 324.84	441.30 (244.30–1420.00)	0.140
Quality of life			
Treatment	698.83 $\pm$ 119.48	650.91 $\pm$ 73.20	0.084
Control	706.35 $\pm$ 118.85	665.35 (598.80–908.50)	0.158

*Significant $P < 0.05$.

at post-test was 685.07 ± 91.45 ($P=0.383$). The comparison of QoL between the control and treatment groups at pretest and post-test are shown in Table 2.

Plasma β -Endorphin Levels

The results of measurements of plasma β -endorphin levels are shown in Table 2. The mean value of β -endorphin levels in the control group at post-test was 512.76 ± 316.02 . The median value of β -endorphin levels in the control group at pretest and post-test was 616.00 (range: 249.10–1392.00) and 441.30 (range: 244.30–1420.00), respectively. Meanwhile, the median value of β -endorphin levels in the treatment group at pretest and post-test was 437.95 (213.90–998.70) and 471.40 (range: 171.30–984.60), respectively. The mean value of β -endorphin levels at pretest and post-test was 571.80 ± 281.13 and 491.14 ± 272.14 , respectively. Meanwhile, the median value of β -endorphin levels at pretest and post-test was 473.95 (range: 213.90–1,392.00) and 454.55 (range: 171.30–1420.00; $P=0.818$), respectively.

Data Availability

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

DISCUSSION

This study found no significant difference in pain scores between pretest and post-test in the control group due to different patients' responses to pain. Many factors affect patients' responses to pain, including physical, mental, social, and spiritual experiences.¹⁴ There were no significant differences after patients taking the pharmaceutical agents due to diverse kinds of cancer-related pain. Acute cancer-related pain is caused by diagnostic and therapeutic factors. Chronic pain, however, has a less-obvious onset and a long and fluctuating course, and is largely driven by CNS sensitization. This is often characterized by flare pain, and like acute pain, chronic pain in cancer can also be caused by cancer therapy or the cancer itself.¹⁵ In addition, patients in the current study received chemotherapy. Chemotherapy causes peripheral neuropathy. Matyh et al. stated that, chemotherapy-related neuropathy arises due to different mechanisms, including impaired tubulin function by chemotherapeutic agents, with cytokine release resulting in degeneration of sensory neurons and sensitization of primary afferent nociceptives.¹⁶ Another study found that, of 100 patients with cervical cancer, 78% felt pain in the previous week, increasing disease stages and pain percentages.¹⁷

The current study found differences in pain-scale ratings before and after therapy in the treatment group. Acupuncture

can be used at all levels of cancer-pain therapy, from postoperative pain, to neuropathy due to chemotherapy, to chronic pain after treatment.¹⁸ In one study, significant decreases in pain intensity after the procedure were higher in an acupuncture group compared to a placebo group.¹⁹ Pain reduction occurs when acupuncture needles are inserted in acupoints, pain receptors on nerve endings are stimulated and cause endogenous opioid secretion, which plays a role in controlling pain. Once the pain-control system is activated, neurons originating from the mesencephalon and periaqueductal gray send their stimuli to the rostral Magnus nucleus and the reticular paragigantocellularis nucleus. Then, these stimuli are delivered to the lateral dorsal column of the spinal cord and their complex inhibitory system.^{20,21}

The current study found no significant difference in pain-scale ratings pretest between the control and treatment groups. Meanwhile, at post-test, there were significant differences in pain-scale ratings between the control and treatment groups. Acupuncture, as part of integrative interventions, can be combined with pharmacologic interventions if necessary. In patients with stage-IIIB cervical cancer who received chemotherapy (50 mg/m²/week of cisplatin), EA at ST 36 4 times with a 1-week interval in between increased their numbers of natural-killer cells, interferon- γ levels, Th1/Th2 ratios, and appetite scores, as well as significantly reducing tumor volumes, pain-score ratings, and nausea scores although these results were not significant.²¹

β -endorphins are produced in the hypothalamus and pituitary gland during excitatory pain, exercise, stress, and orgasms. This neurohormone works as the body's natural antipain agent. Endorphins or endomorphin can cause feelings of pleasure and comfort to get a person energized. Thus far, endorphins have been known as substances that have many benefits. Some of them are: regulating the production of growth and sex hormones; controlling pain; addressing persistent pain, controlling feelings of stress, and enhancing the immune system.²²

There was a significant increase of endorphin-level changes in the treatment group pre- and post therapy.²³ These changes can be caused by plasma β -endorphin levels that are influenced by several other factors and activities. This can include conditions that increase release of endogenous endorphins, such as regular exercise, a calm mind, meditation, laughter, music therapy, sexual activity, feelings of love, and consuming chocolate containing flavonoids, as well as certain conditions that involve low endorphin levels, such as depression, stress, and bodily pain.²⁴

There was no significant differences in post-test β -endorphin levels between the control and treatment groups. This was consistent with a systematic review published from the Support Care Center in 2016.¹¹ In this review, in 2012 patients with cancer, better pain control was

found in the cancer population when acupuncture was combined with analgesic therapy, compared to only with single analgesic therapy.¹¹

The questionnaire used was the EORTC QLQ-C30, which contains 30 questions. This questionnaire is grouped into 15 domains to assess the QoL of patients with cancer. To assess the QoL of patients with cervical cancer in the current study, the Indonesian version of the EORTC QLQ-C30 questionnaire, which had been translated and validated, was used. The pretest and post-test scores of the control group were compared and showed no significant differences. In addition, there were no significant differences in pretest and post-test scores in the treatment group. This was possibly due to the subjectivity of the patients' complaints, given that the EORTC QLQ-C30 questionnaire has been widely used in cancer clinical trials by many research groups and had also been used in non-clinical trial studies.¹³

There were no significant differences in the pretest questionnaire scores between the control group treatment groups. This finding was in accordance with a previous study conducted at the Dr. Hasan Sadikin General Hospital, in Bandung, Indonesia, that overall QoL in patients with cervical cancer undergoing chemotherapy showed a tendency to remain at a moderate level.²⁵

CONCLUSIONS

Cervical cancer is a malignancy mostly in women in developing countries, including Indonesia. Cancer pain is the most common health problem experienced by these patients. Thus far, cancer treatment only uses analgesics, but other alternative treatments are needed. Acupuncture is an alternative therapy that can reduce pain and is almost without side-effects. Acupuncture is safe and easy to implement.

The current study produced significant results in terms of pain-scale ratings, while QoL and β -endorphin levels did not show significant differences between the treatment and control groups. Pain-control therapy, using either drugs or EA produced similar results, but EA, subjectively, induced improvements in pain-scale ratings far more than pharmaceutical treatments.

AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest.

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