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Original Research

Biological Correlates of the Effects of Auricular Point Acupressure on Pain

Chao Hsing Yeh, Ph.D., M.S.N., R.N.[a,*], Nada Lukkahatai, Ph.D., M.S.N., C.N.E., R.N.[b], Xinran Huang, M.P.H[c], Hulin Wu, Ph.D.[c], Hongyu Wang, M.D., Ph.D.[a,d], Jingyu Zhang, B.S.[e], Xinyi Sun, B.S.[e], Thomas J. Smith, M.D.[f]

[a] University of Texas Health Science Center at Houston Cizik School of Nursing
[b] Johns Hopkins University School of Nursing
[c] University of Texas Health Science Center Houston School of Public Health
[d] University of Texas Health Science Center at Houston, McGovern Medical School
[e] Johns Hopkins University Krieger School of Arts and Sciences
[f] Johns Hopkins University School of Medicine

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ABSTRACT

Background:
Aims: To identify candidate inflammatory biomarkers for the underlying mechanism of auricular point acupressure (APA) on pain relief and examine the correlations among pain intensity, interference, and inflammatory biomarkers.
Design: This is a secondary data analysis.
Settings:
Participants/Subjects:
Methods: Data on inflammatory biomarkers collected via blood samples and patient self-reported pain intensity and interference from three pilot studies (chronic low back pain, n = 61; arthralgia related to aromatase inhibitors, n = 20; and chemotherapy-induced neuropathy, n = 15) were integrated and analyzed. This paper reports the results based on within-subject treatment effects (change in scores from pre- to post-APA intervention) for each study group (chronic low back pain, cancer pain), between-group differences (changes in scores from pre- to post-intervention between targeted-point APA [T-APA] and non-targeted-point APA [NT-APA]), and correlations among pain intensity, interference, and biomarkers.
Results: Within-group analysis (the change score from pre- to post-APA) revealed statistically significant changes in three biomarkers: TNF-α (cancer pain in the APA group, $p = .03$), β-endorphin (back pain in the APA group, $p = .04$), and IL-2 (back pain in the NT-APA group, $p = .002$). Based on between-group analysis in patients with chronic low back pain (T-APA vs NT-APA), IL-4 had the largest effect size (0.35), followed by TNF-α (0.29). A strong positive monotonic relationship between IL-1β and IL-2 was detected.
Conclusions: The current findings further support the potential role of inflammatory biomarkers in the analgesic effects of APA. More work is needed to gain a comprehensive understanding of the underlying mechanisms of APA on chronic pain. Because it is simple, inexpensive, and has no negative side effects, APA can be widely disseminated as an alternative to opioids.

Chronic pain is a major health problem (Zelaya et al., 2020) and a primary reason to seek healthcare (Finley et al., 2018). It is the leading cause of disability (The US Burden of Disease Collaborators, 2018) and the most expensive healthcare diagnosis (estimated at $134.5 billion), costing more than cancer, heart disease, and diabetes combined (Dieleman et al., 2020). Individuals with chronic pain often rely on opioids to decrease pain, contributing to the opioid epidemic (Chou et al., 2020; Dalal & Bruera, 2019; Jones et al., 2018; Nahin et al., 2019; Paice, 2018;

* Address correspondence to: Chao Hsing Yeh, Ph.D., M.S.N., R.N., 6901 Bertner Ave., Houston, TX 77030.
E-mail address: chao.hsing.yeh@uth.tmc.edu (C.H. Yeh).

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Paice et al., 2016; Stein et al., 2016; Substance Abuse and Mental Health Services Administration, 2020). Clinical guidelines advocate for nonpharmacologic therapies and self-management of chronic pain (Qaseem et al., 2017; Skelly et al., 2020), but these options are challenging for providers and patients alike.

Acupuncture, a nonpharmacologic therapy, is included in current guidelines to manage chronic pain (Oliveira et al., 2018; Qaseem et al., 2017; Skelly et al., 2020). As of 2020, Medicare covers acupuncture but only for chronic low back pain (Centers for Medicare and Medicaid Services, 2020). When the cost of acupuncture is covered, the insurers often limit the number of visits to control the cost (Heyward et al., 2018). Even with these advances, barriers to implementing acupuncture for pain management exist, including frequent office visits, cost, and lack of access to licensed acupuncturists (Cui et al., 2017; Ledford et al., 2018).

Auricular acupuncture, with origins stemming from traditional (body) acupuncture, is a unique "microsystem" that uses only ear points for treatment. Compared to body acupuncture, it is easier to learn and administer. Paul Nogier, a French neurologist and physician (Nogier, 1981; Nogier, 1987; Nogier, 2014) described a somatotopic representation of the human body on the ears. As part of the system of diagnosis, the presence of active areas on the ear meriting treatment is confirmed by examination of the electrodermal response, via the use of a point finder (Yeh & Huang, 2013). Once identified, active points can be treated classically with acupuncture needles and/or electrical stimulation (Huang, 2005; Oleson, 2014). Another system of treatment is auricular point acupressure (APA) with the use of plant-based vaccaria seeds or metal beads (Yeh & Huang, 2013). Receiving greatest attention worldwide is the use of five classical auricular points for the treatment of addiction by the U.S. National Acupuncture Detoxification Association (2010). The Defense and Veterans Center for Integrative Pain Management and Veterans Health Administration National Pain Management Program have offered battlefield auricular acupuncture training courses for non-acupuncturists to enhance their pain management skills (Niemtzow et al., 2018).

Clinical studies have increasingly demonstrated that auricular acupuncture/APA is emerging as an evidenced-based pain treatment (Abaraogu & Tabansi-Ochuogu, 2015; Asher et al., 2011; Jan et al., 2017; Liu et al., 2015; Moura et al., 2019; Yang et al., 2017; Yeh et al., 2014; Yeh et al., 2019; You et al., 2019; Zhong et al., 2019). Compared to the literature on body acupuncture (Kim et al., 2022; Shi et al., 2020), the literature on the biological mechanisms of the analgesic effects of auricular acupuncture/APA is limited. The gaps between APA effectiveness and mechanistic research have significantly hindered the acceptance of APA by the mainstream health care system and have limited its application in clinical settings.

Stimulation of ear points may cause a broad spectrum of systemic effects, such as modulation of inflammatory cytokine levels, which may explain pain relief (Lin et al., 2015; Yeh et al., 2017; Yeh et al., 2019). Multiple APA studies have shown a decrease in pro-inflammatory cytokines (interleukin [IL]-1β, IL-6, and tumor necrosis factor [TNF]-α) among patients with axial neck pain after anterior cervical discectomy and fusion (Xia et al., 2018), patients with chronic low back pain (Lin et al., 2015), cancer patients with chemotherapy-induced neuropathy (Yeh et al., 2019), and breast cancer patients with aromatase inhibitor-induced arthralgia (Yeh et al., 2017). These finding suggest that the effect of APA on chronic pain might be achieved through neuroimmune signaling. While studies have shown promising findings of the effect of APA on inflammatory biomarkers, the interpretation of these findings is limited owing to the exploratory nature of the studies (small sample size) (Lin et al., 2015; Xia et al., 2018; Yeh et al., 2014; Yeh et al., 2017; Yeh et al., 2019).

Because of the persistent nature of pain in many chronic conditions (e.g., cancer, fibromyalgia, back pain), the underlying mechanism is believed to be modulated by increasing responsiveness of peripheral nociceptive neurons (peripheral sensitization) and nociceptive neurons in the central nervous system (central sensitization) (International Association for the Study of Pain, 2017). To enhance our understanding of the effect of APA on the mechanism of pain relief among patients with chronic pain conditions, we conducted a secondary data analysis of three pilot studies that tested the ability of APA to manage pain among patients with chronic low back pain (n = 61) (Lin et al., 2015), aromatase inhibitor-induced arthralgia (n = 20) (Yeh et al., 2017), and chemotherapy-induced neuropathy (n = 15) (Yeh et al., 2019). The purpose of this secondary data analysis was to further identify candidate inflammatory biomarkers of the mechanisms of APA on pain relief and examine the correlations among pain intensity, interference, and inflammatory biomarkers. In this article, we report the results on within-subject treatment effects (changes in scores from pre- to post-APA intervention) and between-group differences (changes in scores from pre- to post-intervention between targeted-point APA [T-APA] and non-targeted-point APA [NT-APA]), and correlations among pain intensity, interference, and biomarkers.

Methods

Table 1 summarizes the designs, samples, and data collection information of the three pilot studies included (Lin et al., 2015;

Table 1
Summary of the Study Information and Demographic Characteristics.

Study design	Chronic low back pain (n=61)		Arthralgia related to aromatase inhibitors (n=20)	Chemotherapy induced neuropathy (n=15)
	Two groups, randomized controlled trial		One group, open trial	One group, open trial
Intervention	T-APA	NT-APA	T-APA (n=20)	T-APA (n=15)
Age, y	61±17.44	66±16.04		60.20±7.95
Sex				
Male	10 (33%)	10 (32%)	0	4 (27%)
Female	20 (67%)	21 (68%)	20(100%)	11 (73%)
Race/ethnicity, *n* (%)				
White	26 (87%)	25 (81%)	16 (80%)	12 (80%)
Black/African American	4 (13%)	6 (19%)	4(20%)	3 (20%)
Employment situation				
Working	8 (27%)	6 (20%)	9 (45%)	4 (26%)
Not employed (unemployed, retired, homemaker)	22 (73%)	25(80%)	11 (55%)	11 (74%)

T-APA = targeted-point auricular point acupressure; NT-APA = non-targeted-point auricular point acupressure.

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Yeh et al., 2017; Yeh et al., 2019). All three studies were approved by the university's Institutional Review Board. All study participants received interventionist-administered APA weekly for four weeks. Data were collected at pre- and post-intervention. All participants received four weekly APA treatments depending on the assigned study intervention (T-APA or NT-APA). For the low back pain study, the intervention included two study groups (T-APA or NT-APA) (Lin et al., 2015), while the cancer pain study included only the APA intervention (Yeh et al., 2017; Yeh et al., 2019).

APA Treatment Protocol

Intervention group

The APA intervention included one treatment per week for four consecutive weeks. Auricular points on participants' ears were detected with an electrical acupoint finder, which measures auricular cutaneous resistance to identify the potential acupoints for treatment. Ear points for T-APA included three for alleviating stress and pain (i.e., Shenmen, sympathetic, and nervous subcortex) and corresponding points to the anatomical sites (i.e., lower back, foot, or hand), depending on the body symptom (Yeh & Huang, 2013). Bilateral auricular points were identified for treatment. Vaccaria seeds (natural, non-toxic botanical seeds of no medicinal value, $\approx$ 2 mm in diameter) were placed on the ear points for stimulation, and small pieces of waterproof tape ($\approx$ 6 mm^2) were used to secure the seeds onto the ears. In our previously published APA protocol (Lin et al., 2015; Yeh et al., 2017; Yeh et al., 2019), participants were told to press/stimulate the seeds taped to the acupoints on their ears at least three times per day for three minutes each time. The seeds and tape were removed at the end of the fifth day each week to regain point sensitivity prior to the next treatment. The endpoint was the measure of pain intensity and pain interference after the completion of the four-week APA. All study participants received the same APA intervention process.

NT-APA Group

The acupoints selected for the NT-APA group were located away from the site where the participant was experiencing low back pain and included the stomach, mouth, duodenum, and kidney (Yeh & Huang, 2013). Participants in the NT-APA group were blinded to the group assignments.

Measures

Pain intensity and interference

Pain intensity (worst) and pain interference were measured as clinical study outcomes using the Brief Pain Inventory Short Form (BPI-sf) (Cleeland & Ryan, 1994). Worst pain intensity is a 0-10-point numerical rating scale in the past seven days (0 = "no pain at all"-10 "the worst pain ever possible"). The pain interference subscale of the BPI-sf is composed of seven items on a 0-10-point scale assessing the effect of pain on daily function in the past seven days (0 = "Does not interfere"-10 = "Completely interferes). The reliability and validity of the BPI-sf have been cited in more than 400 publications (Cleeland & Ryan, 1994).

Inflammatory Biomarkers

The circulating levels of inflammatory cytokines (IL-1β, IL-2, IL-4, IL-6, IL-10, and TNF-α), β-endorphin, and calcitonin gene-related peptide (CGRP) were measured. The detailed blood sample collection, extraction, and testing processes were published in a previous manuscript (Lin et al., 2015).

Data Analysis

The assumption of the normal distribution of the data was checked. The square-root transformation for the pain interference scores and log-transformation for all biomarkers were used to reduce the skewness of the data before data analyses. Descriptive analysis was used to display the outcomes measurements (including inflammatory biomarkers, pain intensity, and pain interference). Within-subject changes were examined using the changes in scores from pre- to post-intervention for individual subjects in each study group. Between-group differences were examined using the within-subject changes in scores from pre- to post-intervention between the T-APA and NT-APA groups (in only the low back pain study). The Mann-Whitney U Test was used to examine the difference in between-group score changes (T-APA versus NT-APA in the back pain study). Effect size as the standardized differences in the mean between two means (Cohen's d: between-group = the mean score change in the T-APA group compared to the NT-APA group in the low back pain study; within-group = the mean score change from pre-intervention to post-intervention) was calculated to estimate the sample sizes for future randomized controlled trials. The Wilcoxon signed-rank test was performed to test the null hypothesis of no difference in outcome measures between pre- and post-intervention for each study group (within-group difference). Spearman's rank correlation coefficient was used to examine the relationship between clinical outcomes (pain intensity and interference) and biomarkers. Significance was set at a p value $< .05$ for the data analysis and the multiple testing was not adjusted. All data analyses were performed using SAS 9.4 and R-4.2.0.

Results

Characteristics of the Study Participants

In total, 96 study participants were included (n = 61 patients with chronic low back pain, n = 20 breast cancer patients with arthralgia, and n = 15 cancer patients with chemotherapy-induced neuropathy) (Table 1). Most of the study participants were White (82%) and female (68% in the chronic low back pain study and 73% of the cancer patients with chemotherapy-induced neuropathy). Their ages ranged from 35-71 years.

Clinical Outcomes and Biomarkers

Table 2 presents data on clinical outcomes (pain intensity and pain interference) and biomarkers at pre- and post-APA treatment, within-subject changes (the change score between pre- and post-intervention) in biomarkers, pain intensity, and pain interference for each group (T-APA versus NT-APA), and between-group differences (the change in scores between pre- and post-intervention between the T-APA and NT-APA groups in the back pain study). Scores on all the study outcomes (pain intensity, pain interference, and biomarkers) decreased from pre-intervention to post-intervention. The only exceptions were TNF-α and IL-4 in the APA back pain group, whereby TNF-α increased and IL-4 did not change after the intervention.

Within-group Changes in Biomarkers After Intervention

Within-subject analyses revealed statistically significant changes in three biomarkers: TNF-α (cancer pain in the T-APA group, $p = .03$), β-endorphin (low back pain in the T-APA group, $p = .04$), and IL-2 (low back pain in the NT-APA group, $p = .002$). Four biomarkers achieved the change with borderline significance (p value between .05-.10): IL-2 (cancer pain in the

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Table 2
Summary Statistics of Auricular Point Acupressure Effect on Pain Intensity, Pain Interference, and Inflammatory Biomarkers.

Outcomes/Changes		Pre-T-APA	Post-T-APA	Within-Subject Mean Change		Between-Group Difference[a]	
		Mean ± SD	Mean ± SD	Mean ± SD (p value)	Effect Size[b]	Mean ± SD (p value)	Effect Size[a]
Pro-inflammatory Cytokines							
IL-1β	T-APA-Back (n=30)	2.61 ± 0.56	2.54 ± 0.53	-0.07 ± 0.25 (0.14)	-0.12	-0.03 ± 0.19 (0.57)	-0.15
	T-APA-Cancer (n=35)	2.43 ± 1.47	2.39 ± 1.43	-0.04 ± 0.40 (0.48)	-0.03		
	NT-APA (n=31)	2.60 ± 0.62	2.56 ± 0.62	-0.04 ± 0.10 (0.08)	-0.06		
IL-2	T-APA-Back (n=30)	2.71 ± 0.56	2.66 ± 0.52	-0.05 ± 0.28 (0.66)	-0.09	0.02 ± 0.22 (0.78)	0.07
	T-APA-Cancer (n=35)	3.38 ± 0.57	2.98 ± 1.10	-0.40 ± 0.98 (0.06)	-0.45		
	NT-APA (n=31)	2.70 ± 0.69	2.64 ± 0.71	-0.07 ± 0.10 (**0.002**)	-0.09		
IL-6	T-APA-Back (n=30)	3.38 ± 0.51	3.30 ± 0.54	-0.08 ± 0.37 (0.89)	-0.16	-0.01 ± 0.33 (0.89)	-
	T-APA-Cancer (n=35)	3.68 ± 0.79	3.42 ± 1.22	-0.26 ± 0.87 (0.27)	-0.25		0.04
	NT-APA (n=31)	3.45 ± 0.50	3.38 ± 0.53	-0.07 ± 0.29 (0.39)	-0.14		
TNF-α	T-APA-Back (n=30)	4.65 ± 0.36	4.67 ± 0.37	0.02 ± 0.16 (0.99)	0.05	0.05 ± 0.16 (0.27)	0.29
	T-APA-Cancer (n=35)	4.19 ± 0.91	4.09 ± 0.94	-0.10 ± 0.24 (**0.03**)	-0.11		
	NT-APA (n=31)	4.75 ± 0.50	4.72 ± 0.45	-0.03 ± 0.17 (0.19)	-0.06		
Anti-inflammatory Cytokines							
IL-4	T-APA-Back (n=30)	2.79 ± 0.53	2.79 ± 0.55	0.00 ± 0.10 (0.97)	0.01	0.04 ± 0.13 (0.20)	0.35
	T-APA-Cancer (n=35)	2.89 ± 0.32	2.86 ± 0.30	-0.03 ± 0.20 (0.56)	-0.08		
	NT-APA (n=31)	2.71 ± 0.42	2.67 ± 0.37	-0.04 ± 0.15 (0.22)	-0.10		
IL-10	T-APA-Back (n=30)	3.33 ± 0.36	3.26 ± 0.32	-0.06 ± 0.19 (0.08)	-0.18	-0.03 ± 0.20 (0.62)	-
	T-APA-Cancer (n=35)	3.90 ± 0.83	3.69 ± 1.01	-0.21 ± 1.09 (0.18)	-0.23		0.13
	NT-APA (n=31)	3.41 ± 0.36	3.38 ± 0.34	-0.04 ± 0.21 (0.42)	-0.10		
Neuropeptides							
CGRP	T-APA-Back (n=30)	2.62 ± 1.76	2.55 ± 1.63	-0.07 ± 0.38 (0.40)	-0.04	-0.04 ± 0.35 (0.71)	-
	NT-APA-Back (n=31)	2.99 ± 1.31	2.95 ± 1.46	-0.03 ± 0.31 (0.52)	-0.02		0.11
Endorphin	T-APA-Back (n=30)	4.88 ± 0.30	4.82 ± 0.29	-0.06 ± 0.14 (**0.04**)	-0.20	-0.01 ± 0.17 (0.83)	-
	NT-APA-Back (n=31)	4.76 ± 0.29	4.71 ± 0.21	-0.05 ± 0.20 (0.08)	-0.20		0.06
Clinical Outcomes							
Pain	T-APA-Back (n=30)	6.31 ± 1.93	2.44 ± 2.23	-3.88 ± 2.93 (<**0.0001**)	-1.86	-3.05 ± 2.75 (<0.0001)	-
Intensity	T-APA-Cancer (n=35)	6.94 ± 2.46	3.21 ± 2.37	-3.73 ± 2.18 (<**0.0001**)	-1.54		1.11
	NT-APA (n=31)	6.07 ± 1.71	5.24 ± 2.44	-0.83 ± 2.55 (<**0.0001**)	-0.39		
Pain	T-APA-Back (n=30)	2.26 ± 0.46	2.60 ± 1.88	-0.38 ± 0.47 (<**0.0001**)	-0.64	0.23 ± 0.57 (0.12)	0.41
Interference	T-APA-Cancer (n=35)	3.26 ± 2.37	4.36 ± 1.97	-1.29 ± 1.69 (<**0.0001**)	-0.61		
	NT-APA (n=31)	2.12 ± 0.40	2.35 ± 1.51	-0.61 ± 0.66 (<**0.0001**)	-0.91		

[a] Between-group effect size= $(M_t\text{-}M_s)/\sigma_{pooled}$. M_t mean change score for T-APA-Back group, M_s mean change score for NT-APA group (or th. $\sigma_{pooled} = \sqrt{[(n_t\text{-}1)\sigma_t^2+(n_s\text{-}1)\sigma_s^2)/(n_t+n_s)\text{-}2]}$, n_t = the sample size for T-APA-Back group, n_s = the sample size for NT-APA group, σ_t = standard deviation of change score for T-APA-Back group, σ_s = standard deviation of change sccore for NT-APA group.

[b] Within-group effect size= $(M_{post}\text{-}M_{pre})/\sigma_{pooled}$. M_{post} mean score of post-, M_{pre} mean score of pre- (or $\sigma_{pooled} = \sqrt{[(n_{post}\text{-}1)\sigma_{post}^2+(n_{pre}\text{-}1)\sigma_{pre}^2)/(n_{post}+n_{pre})\text{-}2]}$, n_{post} = the sample size for post-, n_{pre} = the sample size for the pre-, σ_{post} = standard deviation of post-, σ_{pre} = standard deviation of of the post-.APA = auricular point acupressure; T-APA = targeted-point APA; NT-APA = non-targeted-point APA; SD = standard deviation; CGRP = calcitonin gene-related peptide; p = Mann-Whitney U Test (between T-APA-Back and NT-APA) and Wilcoxon signed rank test (within-group differences).

T-APA group, $p = 0.06$), IL-10 (low back pain in the T-APA group, $p = 0.08$), IL-1β (low back pain in the NT-APA group, $p = .08$), and β-endorphin (low back pain in the NT-APA group, $p = 0.08$). IL-6 had an effect size of –0.25 while the p value was .27 in the cancer pain APA group.

Between-group Differences

Using the within-group changes in biomarker scores (pre- and post-intervention) between the T-APA and NT-APA groups in the low back pain groups, IL-4 had the largest effect size (0.35), followed by TNF-α (0.29). Three biomarkers had effect sizes greater than 0.10 (IL-1β = 0.15; IL-10 = 0.13; and CGRP = 0.11). Other biomarkers had an effect size smaller than 0.10.

Correlations Among Biomarkers, Pain Intensity, and Pain Interference

Table 3 shows the Spearman's rank correlation coefficients among pain intensity, pain interference, and inflammatory biomarkers on the change in scores after treatment for all subjects. A strong positive monotonic relationship was detected between IL-1β and IL-2 (Spearman's $\rho = 0.66$). Moderate positive monotonic relationships were detected between IL-1β and IL-6 (Spearman's $\rho = 0.41$), between IL-1β and CGRP (Spearman's $\rho = 0.41$), between IL-2 and IL-6 (Spearman's $\rho = 0.48$), between IL-2 and IL-10 (Spearman's $\rho = 0.43$), between IL-6 and IL-10 (Spearman's $\rho = 0.57$), and between TNF-α and IL-10 (Spearman's $\rho = 0.41$). Figure 1 presents the scatter plot for outcome measures with statistically significant Spearman's rank correlation coefficients.

Discussion

The findings of this secondary data analysis from our three pilot studies showed significant improvements in self-reported data (pain intensity and pain interference), significant changes in levels of TNF-α, β-endorphin, and IL-2 from pre- to post-intervention (within-group differences), significant between-group differences in IL-4 and TNF-α (changes from pre- to post-intervention between the T-APA group and NT-APA group), and strong correlations between IL-1β and IL-2, thereby contributing to a better understanding of the role of APA in pain relief via the inflammatory pathway.

The current findings from different chronic pain conditions support the notion that APA may modulate inflammatory biomarkers and consequently lead to the reduction of pain intensity and pain interference.Consistent with other findings, we speculate that APA may affect pain by modulating the type 1 helper T cells and macrophages to reduce pro-inflammatory cytokines that augment pain signals in many chronic pain conditions (Laumet et al., 2019). Peripherally released cytokines also modulate pain signaling and play an important role in the advancement of chronic pain (Andrade et al., 2013; Austin & Moalem-Taylor, 2010). Inhibitors of pro-inflammatory cytokines, such as TNF-α inhibitors (Ohtori et al., 2012) and IL-6 (Ohtori et al., 2012) that reduce cytokine expression, have been used to block chronic pain associated with spinal

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Table 3
Spearman Rank Correlation among Pain Intensity, Pain Interference, and Inflammatory Biomarkers.

Outcomes	IL-2	IL-6	TNF-α	IL-4	IL-10	CGRP	Endorphin	Pain Intensity	Interference
IL-1β	**0.66**[a]	**0.41**[b]	0.09	**0.24**[c]	**0.35**[b]	**0.41**[b]	-.08	-0.09	0.04
IL-2	–	**0.48**[a]	**0.31**[b]	**0.31**[b]	**0.43**[a]	0.26	-.09	-0.11	0.05
IL-6	–	–	**0.29**[b]	0.17	**0.57**[a]	0.08	0.18	-0.06	0.09
TNF-α	–		–	0.19	**0.41**[a]	-.22	0.09	-0.09	-0.09
IL-4		–	–	–	**0.25**[c]	-.05	-.18	-0.02	-0.04
IL-10	–	–	–	–	–	-.01	0.04	0.05	-0.02
CGRP	–	–	–	–	–	–	0.12	-0.11	-0.17
Endorphin	–	–	–	–	–	–	–	0.04	0.06
Pain Intensity	–	–	–	–	–	–	–	–	0.08

[a] p value < 0.0001.
[b] p value < 0.01.
[c] p value < 0.05.

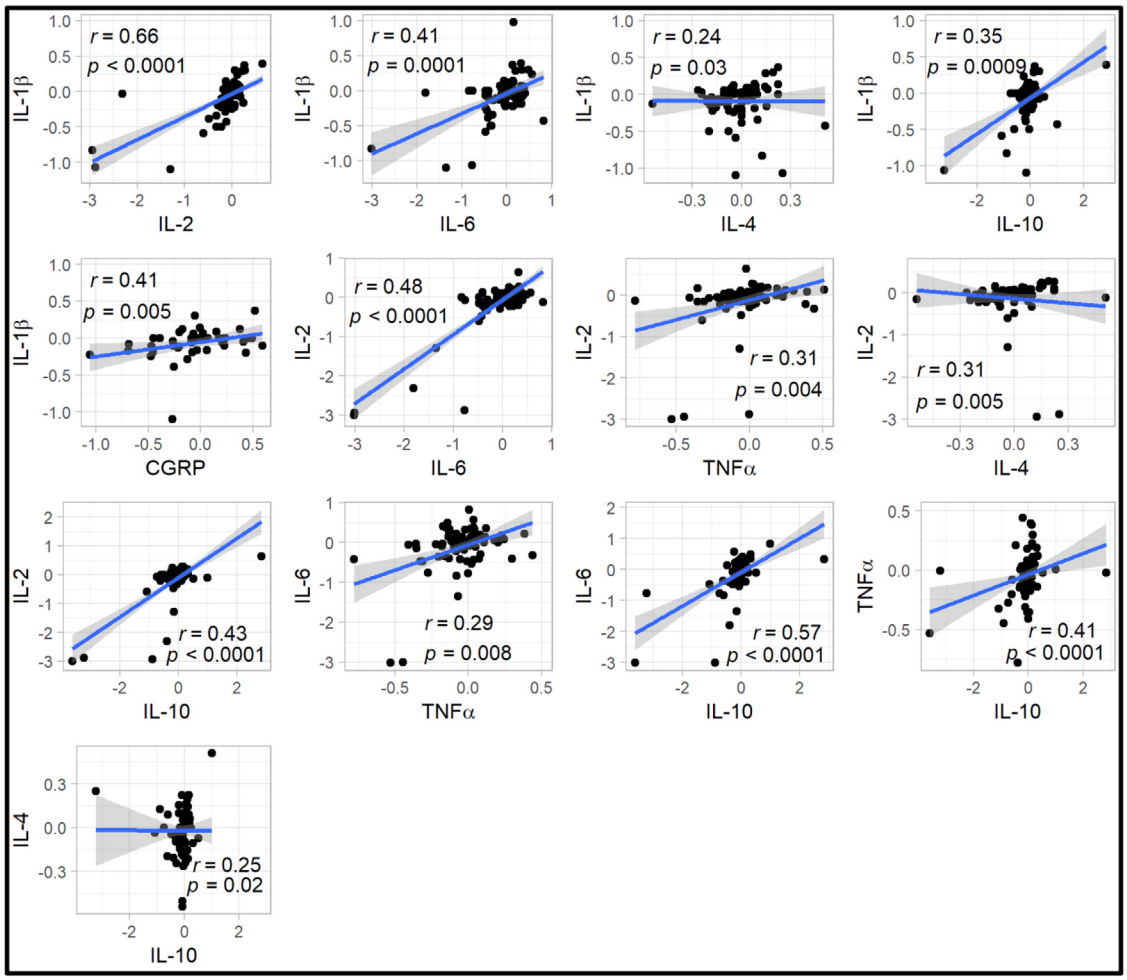

Figure 1. Scatter Plot for Outcome Measures with Statistically Significant Spearman's Rank Correlation. r = Spearman's Rank Correlation Coefficient.

stenosis (Ohtori et al., 2012). While the mechanism of APA on reducing pro-inflammatory cytokines is unclear, we speculate that ear point stimulation causes vasodilation effects via the release of neuropeptide-induced local anti-inflammatory cytokines that could lead to the reduction of pro-inflammatory cytokines. These responses are modulated by mediators of inflammatory biomarkers and could explain the analgesic effects of APA on chronic pain.

While the current analysis enhances our understanding of the effect of APA on inflammatory biomarkers, why the stimulation of the ear points leads to pain relief remains unclear. Recent advances in functional magnetic resonance imaging (fMRI) have provided a useful tool to understand this knowledge gap. For example, stimulation of the ear thumb point produced significant fMRI activity in the thumb region of the somatosensory cortex (Alimi et al., 2002; Romoli et al., 2014), whereas stimulation of a different area of the external ear did not produce the change (Alimi et al., 2002), suggesting the existence of a neurophysiological connection between ear points, corresponding body areas, and the brain (Alimi et al., 2002; Romoli et al., 2014).

Compared with the pain treatments currently available (Qaseem et al., 2020), patients can feel immediate (one-two minutes) pain relief after ear point stimulation (Yeh et al., 2012), making APA an attractive pain treatment. The immediate pain relief from APA has yet to be clearly explained. We previously

conducted an fMRI study to observe brain activity after APA stimulation (Yeh et al., 2020). The results showed that APA can modulate the brain connectivity of the salience network (a brain network for the integration of sensory, emotional, and cognitive information) (Uddin, 2016), the executive control network (a key network in top-down cognitive control processes, such as decision making and emotion regulation) (Goldman-Rakic, 1995), and the basal ganglia network (a crucial network for a variety of motor and cognitive functions) (Afifi, 2003). These findings provide a theoretical basis for the neural mechanism of APA in pain processing. We speculate that overlapped cutaneous nerves in the outer ear (i.e., auricular branch of the vagus nerve, the auriculotemporal nerve, and the great auricular nerve) correspond to specific areas of the brain to confer immediate pain relief from ear point stimulation. Specifically, we posit that these areas have a reflex connection with specific parts of the body, and that stimulating ear points provides therapeutic effects.

Implications for Nursing and Pain Management

The current findings advance our basic scientific understanding of the inflammatory pathway underlying the effects of APA on pain relief and could facilitate the acceptance of APA by mainstream healthcare providers. Unlike acupuncture, which is a passive treatment, APA is a noninvasive, low-cost technique and engages patients to apply pressure to points on their ears to self-manage pain anywhere, anytime. Moreover, compared to acupuncture, APA is more accessible to patients because it can be administered by health practitioners with brief training and is feasible to scale up. APA is not yet widely available in U.S. healthcare systems, and we received an overwhelming number of requests from former study participants for further APA treatment. To scale up, maximizing the usability and accessibility of APA, we have conducted pilot studies using a smartphone app to support self-administered APA for pain, which featured instructional and demonstrational videos (Kawi et al., 2021; Yeh et al., 2021). The four-week intervention demonstrated the feasibility of APA to support self-management of pain among patients with chronic pain (Kawi et al., 2021; Yeh et al., 2021). The current study sets the foundation for future work to test the endogenous biomarkers and critically elucidate the mechanism of APA on pain relief.

Limitations

Because of the complex interaction among inflammatory biomarkers in chronic pain (Iyengar et al., 2017; Mizher et al., 2020; Schou et al., 2017; Uceyler et al., 2006), the study findings should be interpreted in light of limitations, including the nature of the secondary data analysis (i.e., the combination of data from different chronic pain conditions), a lack of comparison of APA data in the cancer pain group, a lack of long-term follow-up data (i.e., only pre- and post-intervention data were included), and a lack of the control of confounding in inflammatory biomarkers. For example, cytokines and chemokines have short half-lives that vary from two-six hours (Oda et al., 2005), and information regarding circadian rhythms and other clinical characteristics (e.g., acute illness/ trauma, immune disease, medication use, nutrition, endocrine/metabolic disease) was not available.

Conclusions

Based on our findings, APA shows great promise to reverse chronic pain through an inflammatory mechanism, i.e., it exhibits anti-inflammatory efficacy by blocking pro-inflammatory cytokines (TNF-α, IL-2) or releasing anti-inflammatory cytokines (IL-4) or β-endorphins. More work is needed to understand the complex nature of these biological, psychophysiological, and genetic relationships. Future larger-scale research should investigate the effect of these biomarkers on the analgesic effects of APA in a rigorous mechanism study using a randomized control trial and ear point specificity-control.

Declaration of interests

None.

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