Do different doses of acupuncture matter on autonomic nervous activity and symptom management in dysmenorrhea? A randomized controlled trial.

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Abstract

Background The study examined whether the acupuncture dose (number of acupoints stimulated) impacted the efficacy of acupuncture on dysmenorrhea and the relationship with autonomic nervous system regulation.

Methods This three-arm randomized controlled study included a high-dose acupuncture (12 acupoints, N = 23), low-dose acupuncture (6 acupoints, N = 30) and control (N = 30) arm. The treatment course was three months. We set heart rate variation (HRV) and analgesics dependence as the primary outcome measurements; Visual Analog Scale (VAS) score, Verbal Multidimensional Scoring System (VMSS) and the 12-Item Short Form Health Survey (SF-12) quality of life questionnaires were set as secondary outcomes. SPSS version 24 was used for data analysis.

Results Low-dose acupuncture was superior to high-dose in analgesics dependence (p value: low/high/control: p = 0.043/p = 0.056/p = 0.376); symptom relief (VMSS: low/high/control: p < 0.001/p = 0.007/p = 0.109); and physical quality of life (low/high/control: p < 0.001/p = 0.01/p = 0.007). The groups did not differ in HRV parameters (p > 0.05). In intergroup analysis, more significant changes were noted in the high-dose than in the low-dose group. The scattered nature of the significant changes implies that acupuncture may have a short-term effect on HRV parameters which does not correlate with the acupuncture dose.

Conclusions Acupuncture can effectively treat dysmenorrheal pain, improve symptoms and reduce analgesic dependence, but the effect does not correlate with the number of acupoints stimulated. The acupuncture has short-term effect on HRV; yet whether its efficacy on dysmenorrhea is directly related to adjusting the autonomic nervous system may need more large-scale study. It is a safe and effective alternative therapy for dysmenorrhea.

Trial: The Efficacy of Different Doses of Acupuncture in Dysmenorrhea, NCT03881319 at ClinicalTrials.gov,

Background

Dysmenorrhea is a sort of period pelvic pain caused by an abrupt decrease in blood flow and ischemia due to frequent contraction of the uterus. Many females are afflicted with dysmenorrhea to different extents. Some suffer from depression and reduced quality of life while others may even need to withdraw from work or school because of their impaired ability to perform daily activities(1). Thus, dysmenorrhea represents a huge, but hidden, health burden and is worthy of our attention.

The prevalence of dysmenorrhea varies from 34–94%(2). Generally speaking, primary dysmenorrhea is menstrual pain in the absence of pelvic pathology, while secondary dysmenorrhea is caused by organic dysfunction such as endometriosis, uterus malformation, cervix structure, pelvic inflammation, or other conditions(3). In clinical practice, gynecologists apply analgesics such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and oral contraceptive pills (OCT) or progestin as conventional therapy(4). More than two-thirds of women with dysmenorrhea take analgesics(5) and nearly 80% have adopted some complementary therapy, such as herbal medicine, acupuncture, moxibustion or aromatherapy. As NSAIDs may cause gastrointestinal discomfort or dyspepsia and hormone therapy can lead to other concerns, some women now adopt acupuncture as a safer therapeutic alternative(6, 7). Women who adopt acupuncture as an alternative therapy usually wish to withdraw the medication use or improve their pain and other symptoms in order improve their quality of life.(8) As acupuncture has been widely used in dysmenorrhea, we observe that people expect greater efficacy with the use of more needles of stimulation; however, the relationship of acupoint selection and optimal treatment is not established(9). No study has yet compared the efficacy of different schedules of acupoints in treating dysmenorrhea, and the acupoints used differ in different trials. We therefore wanted to evaluate whether the number (or dose) of acupoints would affect the outcomes of acupuncture in dysmenorrhea.

Furthermore, in terms of the mechanism of acupuncture, the symptoms related to dysmenorrhea such as anxiety, insomnia and diarrhea are non-specific and related to autonomic dysfunction, namely, vago-sympathetic tone imbalance(10). A previous study also noted that women with dysmenorrhea had decrease heart rate variation (HRV) and autonomic dysfunction compared with the control group(11). Research confirmed that dysmenorrhea afflicted pain and lowered high frequency (HF), indicting lower parasympathetic tone and increasing sympathetic tone(12), compatible with disharmony in the yin/yang. As acupuncture has proven efficacy in adjusting autonomic dysfunction(13, 14) and treating dysmenorrhea(7, 15), we sought to understand whether the effect of acupuncture in dysmenorrhea was related to adjustments in the autonomic nervous system. Lastly, we wanted to know if acupuncture could help women with dysmenorrhea take fewer NSAIDs or improve their quality of life.

According to the theory of Traditional Chinese Medicine, acupuncture regulates the energy of the meridians and coordinates the balance of yin/yang(16, 17). Western medicine interprets the mechanism of pain control of acupuncture as an effect of neurophysiology(18) and the release of neuropeptides such as endorphin(19). Additionally, in our previous study, we noted that the theory of yin/yang (meridian) is compatible with the autonomic nerve theory(20). Therefore, in this clinical trial, we aim to evaluate: 1) the effect of different acupuncture doses (by number of acupoints) in dysmenorrhea; 2) the relationship of the mechanism of acupuncture with the adjustment of autonomic nerve activity in dysmenorrhea; and 3) the effect of acupuncture on analgesic dependence in women with dysmenorrhea.

Methods

Subjects and Allocation

We selected the participants according to the inclusion criteria: 1) a diagnosis of primary dysmenorrhea according to the Primary Dysmenorrhea Consensus Guideline(21); 2) age from 16 to 35 years without history of delivery; 3) normal menstrual cycle (28 ± 7 days and duration 7 ± 3 days); and 4) menstrual pain scoring more than 40 on a 100-point Visual Analog Scale (VAS) during the baseline menstrual period according to the patient-kept dairy. The main exclusion criteria were: 1) secondary dysmenorrhea related to endometriosis, endometrial polyps, pelvic inflammatory disease or uterine myoma; and 2) other

gynecological problems. Patients enrolled in the acupuncture group were allowed to take NSAIDs at their usual usage and record the dosage in a painkiller diary which was collected.

In total, 83 patients were included in the acupuncture (high-dose: 12 acupoints: N=23; low-dose: 6 acupoints, N=30) and control (N=30) groups from 01, June, 2018 to 31, Dec. 2019. Patients were allowed to receive acupuncture or medication as their intention, yet those in the intervention groups were randomized to different doses (number of acupoints) of acupuncture by using random allocation software 2.0. Sequentially numbered containers were performed, all of the containers were tamper-proof, equal in weight, and similar in appearance. The study was performed in Traditional Medicine and Gynecological Departments, Taipei City Hospital from March 2019 to Dec. 2019. The trial was approved by the hospital Institutional/Independent Review Board (approval no. TCHIRB 10701111). The trial is registered at ClinicalTrials.gov, with number of NCT03881319. Figure 1 provides a flow chart of subject recruitment.

Intervention

In the acupuncture group, patients received acupuncture twice in each luteal phase, for three consecutive menstrual cycles, represented as Acupuncture 1-1; 1-2; 2-1, etc. The acupoints selected by following the Traditional Chinese Medicine and meridian theory in the low-dose group were: PC6 (內關), SP4 (公孫), SP6 (三陰交), SP10 (血海), RN4 (關元) and RN6 (氣海). Those selected for the high-dose group were the acupoints for the low-dose group, plus: RN3 (中極), LI4 (合谷), ST36 (足三里), KI3 (太谿), LR3(太衝) and EX-CA1 (子宮) (Figure 2). De-qi sensation(22) was manipulated with 20 mins of stimulation in each treatment session, using sterile disposable acupuncture needles. In the control (medication) group, participants took only NSAIDs with or without OCT. Patients in the acupuncture groups were allowed to take NSAIDs if they still felt pain and were asked to record the dosage used. The study included at least three consecutive menstrual cycles of treatment.

Outcome measures

To investigate the effect of acupuncture on autonomic function, we used HRV and analgesics dosage as the primary outcomes to assess the relationship and effect of different doses (number of acupoints stimulated) on autonomic nervous status and analgesic dependence. The HRV parameters included the time domain and frequency domain, before and after each course of intervention in both groups. To compare treatment efficacy by group, we used the VAS score to measure pain; the verbal multidimensional scoring system (VMSS), which asks participants to grade their ability to work, their systemic symptoms and their analgesics taking; and the 12-Item Short Form Health Survey (SF-12) quality of life questionnaire as secondary outcomes measurements.

Statistical analysis

In this trial, the estimated sample size was 34 in each group which determined by G power software, with z score:1.96, margin of error(e=0.1) , and the statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY). The data analysis was based on the intention-to-treat population. Means and standard deviations were determined for all data. We applied one-way ANOVA to compare the effect of acupuncture in the acupuncture and control groups, while the chi-squared test was used to analyze the categorical variables. The level of significance was established as P <=0.05; 95% confidence interval).

Results

In total, 98 patients were enrolled in the trial, 83 completed the trial: 23 in the high-dose group, 30 in the low-dose group and 30 in the control group. During the trial, no participants had any side effect from the intervention or treatment. Table 1 reveals no significant difference in baseline characteristics or HRV parameters between groups.

Table 1
The characteristics of participants in the study

	Acupuncture high dose group (N = 23)	Acupuncture low dose group(N = 30)	Control group(N = 30)	p value
	Mean (SD)	Mean (SD)	Mean (SD)	
Basic data				
Age(year)	34.3(5.8)	33.1(7.3)	32.0(8.3)	.537
Body mass index(kg/m$^{2)}$)	22.4(3.9)	23.8(5.8)	21.6(3.3)	.180
SBP(mmHg)	72.0(3.6)	71.5(5.1)	71.8(6.7)	.907
DBP(mmHg)	108.3(7.2)	108.1(7.5)	107.2(12.3)	.949
Heart rate(times/min)	74.0(9.9)	71.4(6.9)	73.8(10.5)	.476
Menstruation related data				
Age at menarche(years)	12.4(1.3)	12.9(1.6)	12.4(1.7)	.343
Menstrual cycle duration(days)	30.3(3.3)	28.9(1.2)	29.5(1.9)	.098
Menstrual irregularity, n(%)	1(4.3%)	5(16.7%)	4(13.3%)	.380
menstrual pain scores (VAS)	5.3(1.5)	5.9(1.6)	5.6(1.8)	.335
Severity of dysmenorrhea (VMSS)				
Grade 0–1: not painful or mild pain	7(30.4%)	4(13.3%)	8(26.7%)	.281
Grade 2–3:moderate pain or severe pain	16(69.6%)	26(86.7%)	22(73.3%)	
Initial onset of menstrual pain, n(%)				
Menarche	6(26.1%)	10(33.3%)	7(23.3%)	.160
< 3 years after menarche	1(4.3%)	3(10.0%)	8(26.7%)	
Others	16(69.6%)	17(56.7%)	15(50.0%)	
Use of medicine regulating menstruation, n(%)	5(21.7%)	12(40.0%)	9(30.0%)	.358
Painkillers (mg)	173.9(387.6)	741.7(1467.3)	291.7(549.6)	.075
HRV-related parameters				
SDNN(ms)	43.0(15.9)	46.9(15.7)	45.8(27.8)	.785
R-MSSD(ms)	36.6(16.5)	41.5(17.3)	43.7(26.4)	.465
PNN50(%)	18.7(17.3)	23.0(19.2)	21.5(21.5)	.727
LF (%)	53.1(16.0)	48.9(19.8)	57.3(14.8)	.169
LF (ms2)	381.5(273.8)	489.3(725.3)	908.5(1555.4)	.145
HF (%)	46.9(16.0)	51.1(19.8)	42.7(14.8)	.169
HF (ms2)	372.6(318.1)	505.9(418.9)	576.4(685.1)	.356
LF/HF	1.44(1.00)	1.44(1.44)	1.84(1.98)	.543
VLF (ms2)	1333.7(1193.8)	1447.1(1071.6)	1363.8(1703.0)	.950
TP(ms2)	2087.8(1561.3)	2442.3(1518.4)	2848.6(3773.2)	.566
SF-12 quality of life scores				
PCS	42.4(8.6)	41.5(7.6)	42.2(6.9)	.904
MCS	32.9(7.8)	36.8(11.9)	35.9(9.3)	.356
SBP: systolic blood pressure.				
DBP: diastolic blood pressure.				
VAS: visual analogue scale score.				
VMSS: verbal multidimensional scoring system.				
SDNN: standard deviation of adjacent peak-to-peak (NN) intervals				

	Acupuncture high dose group (N = 23)	Acupuncture low dose group(N = 30)	Control group(N = 30)	*p* value
	Mean (SD)	Mean (SD)	Mean (SD)	
R-MSSD: root-mean square of differences of successive RR intervals				
pNN50: % of differences of adjacent RR intervals > 50 ms				
LF: low frequency band in absolute and normalized values.				
HF: high frequency band in absolute and normalized values				
LF/HF: low frequency/high frequency ratio				
VLF: very low frequency band in absolute and normalized values.				
TP: variance of NN intervals in FFT analysis.				
PCS: physical health composite score.				
MCS: mental health composite score.				
p < 0.05, ** *p* < 0.01, *** *p* < 0.001				

The effect of acupuncture dosage on heart rate variation (HRV) parameters

Table 2 compares the change in HRV parameters before and after treatment in the acupuncture and control groups. No significant difference was noted before and after the patients in control group who took 3 months of medication for their dysmenorrhea (p > 0.05). A similar phenomenon was noted in the acupuncture groups, with no significant change noted in patients' HRV parameters in the high-dose group, yet some meaningful improvement was found in the low-dose acupuncture group in both time and frequency domains (i.e., the percent of differences of adjacent RR intervals > 50 ms, p = 0.04; the percentage of low frequency bands, p = 0.032; and the percentage of high frequency bands, p = 0.032).

Table 2
The changes in autonomic nervous activity status before and after the intervention.

	Acupuncture high dose group (N = 23)			Acupuncture low dose group (N = 30)			Control group(N = 30)		
	Baseline Mean (SD)	After 3 months Mean (SD)	p	Baseline Mean (SD)	After 3 months Mean (SD)	p	Baseline Mean (SD)	After 3 months Mean (SD)	p
Time Domain									
SDNN	43.0(15.9)	41.0(14.0)	.580	46.9(15.7)	46.8(15.7)	.974	45.8(27.8)	48.0(17.0)	.530
R-MSSD(ms)	36.6(16.5)	35.2(17.2)	.711	41.5(17.3)	36.4(14.0)	.054	43.7(26.4)	45.9(22.1)	.567
PNN50(%)	18.7(17.3)	15.4(15.6)	.382	23.0(19.2)	16.4(14.3)	.040*	21.5(21.5)	22.1(18.2)	.830
Frequency Domain									
LF (%)	53.1(16.0)	50.7(17.3)	.474	48.9(19.8)	55.8(19.3)	.032*	57.3(14.8)	50.4(15.4)	.056
LF (ms2)	381.5(273.8)	394.5(395.7)	.868	489.3(725.3)	503.1(426.0)	.929	908.5(1555.4)	430.4(273.8)	.082
HF (%)	46.9(16.0)	49.3(17.3)	.474	51.1(19.8)	44.2(19.3)	.032*	42.7(14.8)	49.6(15.4)	.056
HF (ms2)	372.6(318.1)	358.1(316.8)	.866	505.9(418.9)	375.0(311.0)	.084	576.4(685.1)	554.1(578.8)	.823
LF/HF	1.44(1.00)	1.36(1.04)	.721	1.44(1.44)	1.96(2.04)	.189	1.84(1.98)	1.23(0.76)	.103
VLF (ms2)	1333.7(1193.8)	1115.3(681.5)	.356	1447.1(1071.6)	1549.9(1475.3)	.778	1363.8(1703.0)	1601.0(1099.5)	.295
TP(ms2)	2087.8(1561.3)	1868.0(1127.2)	.513	2442.3(1518.4)	2428.0(1820.6)	.975	2848.6(3773.2)	2585.5(1827.1)	.628

SDNN: standard deviation of adjacent peak-to-peak (NN) intervals.

R-MSSD: root-mean square of differences of successive RR intervals.

pNN50: % of differences of adjacent RR intervals > 50 ms.

LF: low frequency band in absolute and normalized values.

HF: high frequency band in absolute and normalized values.

LF/HF: low frequency/high frequency ratio.

VLF: very low frequency band in absolute and normalized values.

TP: variance of NN intervals in FFT analysis.

*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Despite the lack of obvious difference in between-group analysis, the intergroup-analysis of the acupuncture groups (Table 3) showed that patients had some improvement in autonomic nervous activity after certain acupuncture treatments. For example, in the high-dose acupuncture group, the Standard Deviation of Normal to Normal (SDNN, represents overall heart rate variability index) significantly changed after acupuncture session 1−1 (first menstrual cycle, first acupuncture session, p = 0.015); session 2 − 1 (p = 0.016); session 2−2 (p = 0.025); and session 3 − 1 (p = 0.031). HF (represent parasympathetic tone) significantly increased after sessions 2−2 (p = 0.042) and 3 − 1 (p = 0.025). Total power (TP), which represent autonomic activity, significant improved after sessions 1−1 (p = 0.013), 2 − 1 (p = 0.019) and 2−2 (p = 0.035). However, the significance of these changes was less in the low-dose acupuncture group. Nevertheless, the significant change distribution implied that acupuncture might have a short-term effect on some HRV parameters, but there was no obvious tendency of superiority for either high- or low-dose acupuncture (Table 3).

Table 3
The comparison of short-term effect reflecting in each acupuncture session (intergroup- analysis) Valu

		High dose (N = 23)	Low dose (N = 30)	High dose (N = 23)	Low dose (N = 30)	High dose (N = 23)	Low dose (N = 30)	High dose (N = 23)	Low dos (N = 30)
SDNN (ms)	B	43.0(15.9)	46.9(15.7)	43.2(17.2)	45.4(12.0)	42.5(15.7)	43.3(18.3)	41.4(13.6)	45.0(19.4
	A	50.4(21.3)	47.0(16.6)	47.7(19.6)	49.5(17.4)	49.0(18.0)	49.9(14.6)	48.8(17.0)	47.9(13.0
	p	.015*	.976	.199	.121	.016*	.031*	.025*	.309
R-MSSD (ms)	B	36.6(16.5)	41.5(17.3)	37.2(19.4)	41.1(15.8)	36.4(17.0)	37.1(20.7)	35.4(19.4)	38.9(20.9
	A	42.9(21.1)	44.0(19.1)	40.7(17.1)	44.4(19.3)	42.9(22.9)	41.1(16.8)	42.2(20.9)	41.1(15.1
	p	.010*	.304	.219	.153	.040*	.226	.087	.479
PNN50 (%)	B	18.7(17.3)	23.0(19.2)	17.8(19.6)	22.7(17.9)	16.2(14.1)	18.3(20.8)	15.4(18.6)	19.8(20.8
	A	25.1(20.8)	24.4(19.3)	21.8(17.7)	25.2(20.0)	23.3(21.3)	22.7(17.8)	22.1(20.2)	22.0(18.1
	p	.008**	.581	.219	.304	.021*	.175	.089	.439
LF (%)	B	53.1(16.0)	48.9(19.8)	53.9(10.9)	50.6(15.5)	55.3(17.5)	48.9(17.8)	52.5(18.6)	48.6(17.9
	A	52.6(16.2)	45.2(18.0)	53.0(16.0)	48.5(17.9)	51.7(16.8)	50.3(15.8)	48.5(15.3)	50.2(17.4
	p	.870	.278	.691	.585	.317	.693	.122	.604
LF (ms2)	B	381.5(273.8)	489.3(725.3)	358.6(275.2)	420.1(254.7)	388.0(307.1)	351.9(315.3)	368.8(333.2)	415.0(43
	A	559.8(550.1)	502.5(513.9)	520.2(500.4)	589.4(550.5)	527.2(430.0)	528.6(437.6)	504.7(523.4)	558.8(72
	p	.069	.932	.097	.046*	.011*	.050	.165	.318
HF (%)	B	46.9(16.0)	51.1(19.8)	46.1(10.9)	49.4(15.5)	44.7(17.5)	51.1(17.8)	47.5(18.6)	51.4(17.9
	A	47.4(16.2)	54.8(18.0)	47.0(16.0)	51.5(17.9)	48.3(16.8)	49.7(15.8)	51.5(15.3)	49.8(17.4
	p	.870	.278	.691	.585	.317	.693	.122	.604
HF (ms2)	B	372.6(318.1)	505.9(418.9)	362.0(373.2)	461.0(347.7)	381.3(393.4)	413.7(442.9)	389.7(421.0)	447.0(46
	A	469.9(354.4)	583.2(541.4)	469.5(498.4)	536.9(414.7)	497.7(482.7)	531.1(472.5)	541.4(504.1)	496.0(43
	p	.072	.272	.152	.187	.107	.192	.042*	.593
LF/HF	B	1.44(1.00)	1.44(1.44)	1.30(0.61)	1.30(0.99)	1.71(1.43)	1.29(1.08)	1.62(1.50)	1.29(1.1
	A	1.48(1.30)	1.21(1.35)	1.53(1.39)	1.34(1.38)	1.34(0.97)	1.33(1.13)	1.17(0.86)	1.51(1.7
	p	.865	.336	.329	.884	.212	.885	.052	.373
VLF (ms2)	B	1333.7(1193.8)	1447.1(1071.6)	1426.9(1111.9)	1319.9(670.6)	1271.9(912.2)	1434.1(1373.0)	1127.7(716.1)	1524.2(1
	A	1946.8(1955.1)	1393.7(884.0)	1648.4(1773.8)	1618.8(1243.4)	1681.9(1242.5)	1636.1(1143.0)	1613.7(1132.5)	1403.3(8
	p	.043*	.828	.462	.187	.104	.302	.068	.572
TP (ms2)	B	2087.8(1561.3)	2442.3(1518.4)	2147.4(1578.7)	2200.9(1037.6)	2041.2(1472.5)	2199.7(1939.0)	1886.1(1257.7)	2386.2(2
	A	2976.5(2395.3)	2479.4(1702.2)	2638.1(2203.3)	2745.1(1851.4)	2706.8(1725.4)	2695.8(1550.6)	2659.9(1751.6)	2458.1(1
	p	.013*	.915	.190	.048*	.019*	.114	.035*	.817

B: before acupuncture.

A: after acupuncture.

SDNN: standard deviation of adjacent peak-to-peak (NN) intervals.

R-MSSD: root-mean square of differences of successive RR intervals.

pNN50: % of differences of adjacent RR intervals > 50 ms.

LF: low frequency band in absolute and normalized values.

HF: high frequency band in absolute and normalized values.

LF/HF: low frequency/high frequency ratio.

VLF: very low frequency band in absolute and normalized values.

TP: variance of NN intervals in FFT analysis.

	High dose (N = 23)	Low dose (N = 30)	High dose (N = 23)	Low dose (N = 30)	High dose (N = 23)	Low dose (N = 30)	High dose (N = 23)	Low dos (N = 30)
Acupuncture 1−1(A1-1): first week of 1st cycle.								
Acupuncture 1−2(A1-2): second week of 1st cycle.								
Acupuncture 2 − 1(A2-1): first week of 2nd cycle.								
Acupuncture 2−2(A2-2): second week of 2nd cycle.								
Acupuncture 3 − 1(A3-1): first week of 3rd cycle.								
Acupuncture 3 − 2(A3-2): second week of 3rd cycle.								
*p < 0.05, ** p < 0.01, *** p < 0.001								

The effect of acupuncture dosage on reducing analgesics dependency and Quality of Life

As for use of painkillers, acupuncture could significantly reduce the level of painkiller or analgesic use after 3 months' treatment and low-dose acupuncture had a more significant benefit (p = 0.043) than high-dose acupuncture (p = 0.056). No significant change was noted in the control group (p = 0.376).

Furthermore, high-dose acupuncture (p < 0.001), low-dose acupuncture (p < 0.001) and medication (p < 0.001) all had a significant effect on relief of pain, as reflected in the VAS scores. The difference between the three groups not reach significance (p = 0.145). In terms of quality of life as measured by the SF-12, low-dose acupuncture improved participants' physical component score (PCS) much more meaningfully then did high-dose acupuncture (low-dose: p < 0.001; high-dose: p = 0.001; control: p = 0.007). In the mental component score (MCS), high-dose acupuncture was superior to the other two groups, which implies a placebo effect (high-dose: p < 0.001; low-dose: p = 0.025; control: p = 0.01) (Table 4).

Table 4
The improvement of analgesics dependence, pain (VAS), Quality of Life (SF12) and VMSS in acupuncture (high/low dose) and control group

	Acupuncture high dose group (N = 23)			Acupuncture low dose group (N = 30)			Control group(N = 30)		
	Baseline Mean (SD)	After 3 months Mean (SD)	p	Baseline Mean (SD)	After 3 months Mean (SD)	p	Baseline Mean (SD)	After 3 months Mean (SD)	p
Painkillers (mg)	173.9(387.6)	43.5(144.1)†	.056	741.7(1467.3)	216.7(386.9)	.043*	291.7(549.6)	416.7(732.1)	.376
VAS	5.3(1.5)	3.1(1.9)	< 0.001***	5.9(1.6)	3.0(1.4)	< 0.001***	5.6(1.8)	3.9(2.3)	< 0.001***
SF-12									
PCS	42.4(8.6)	49.5(6.4)	.001**	41.5(7.6)	47.9(5.2)	< 0.001***	42.2(6.9)	45.9(6.4)	.007**
MCS	32.9(7.8)	40.6(11.6)	< 0.001***	36.8(11.9)	41.5(9.0)	.025*	35.9(9.3)	39.3(9.1)	.010*
	Acupuncture high dose group (N = 23)			Acupuncture low dose group (N = 30)			Control group(N = 30)		
VMSS	Baseline N (%)	After 3 months N (%)	p	Baseline N (%)	After 3 months N (%)	p	Baseline N (%)	After 3 months N (%)	p
Grade 0−1	7(30.4%)	18(78.3%)	.007**	4(13.3%)	19(63.3%)	< 0.001***	8(26.7%)	14(46.7%)	.109
Grade 2−3	16(69.6%)	5(21.7%)		26(86.7%)	11(36.7%)		22(73.3%)	16(53.3%)	
VAS: visual analogue scale score									
QoL: quality of life									
PCS: physical health composite score.									
MCS: mental health composite score.									
VMSS: Verbal multidimensional scoring system.									
Grade 0−1: menstruation is not painful or mild pain.									
Grade 2−3: Menstruation is moderate pain or severe pain.									
*p < 0.05, ** p < 0.01, *** p < 0.001									

The effect of different doses of acupuncture on dysmenorrhea symptoms

In terms of severity of dysmenorrhea scores, patients in both acupuncture groups has significant improvement in VMSS scores. Low-dose acupuncture was more efficient in relieving symptoms than high-dose acupuncture (high-dose: p = 0.007; low-dose: p < 0.001; control: p = 0.109) (Table 4).

Discussion

Dosage effect

This is not the first study to confirm the efficacy of acupuncture in reliving primary dysmenorrhea(23, 24). However, few studies have evaluated the efficacy of different doses of acupuncture or the use of more acupoints. Acupuncture has been widely applied to diverse conditions: pain, arthritis, neuropathy, insomnia, and even some cancer-related side effects(25, 26). However, scholars and clinical physicians have not yet reached consensus on the optimal acupuncture prescription, including the number of acupoints, the number of acupuncture sessions, or even the location of acupoints or the optimal total dose. A study by Sun et al. (2019) pointed out that a higher dosage of acupuncture might provide better treatment outcomes in terms of relief of pain and dysfunction in patients with knee osteoarthritis(27), but others consider that more acupuncture sessions will only relieve symptoms in those with chronic pain(28). In primary dysmenorrhea, only one previous study has demonstrated that the timing of the acupuncture treatment and the mode of needle stimulation were germane to menstrual pain outcomes, but even this study failed to identify the optimum dose parameters for this condition(29). From our study, we noted that, when the parameters of acupuncture timing and frequency were fixed, acupuncture with fewer acupoints (lower dose) was not inferior to higher dose, and even better in terms of dependence on analgesics (6 acupoints: 0.043; 12 acupoints: 0.056); dysmenorrhea symptom control (VMSS: 6 acupoints: p<0.001; 12 acupoints: p=0.007); and quality of life (SF-12 PCS: 6 acupoints: p<0.001; 12 acupoints: p=0.001). Therefore, the clinical physician should understand that clinical efficacy is not depend on the number of acupoints and should convey this concept to patients, to reduce the waste of medical resources(9). In quality of life assessment, we found that subjects had more improvement in mental quality of life than in physiological quality of life, so that the placebo effect should be considered a relevant psychological factor. In this regard, a study claimed that the correlation coefficients between de-qi and the therapeutic efficacy of acupuncture were greater than those between psychological factors and therapeutic efficacy in dysmenorrhea(30). Therefore, the mechanisms driving acupuncture efficacy are complex and extend beyond the simplistic "more is better" concept of treatment.

Relationship to autonomic activity adjustment

Some studies indicate that de-qi is the most important factor in making acupuncture effective(31). A study in 2017 revealed that patients with dysmenorrhea who experienced actual de-qi sensation had more pain relief and a greater analgesic effect(32). An interesting study revealed that de-qi elicited a significant response to acupuncture in specific brain regions, indicating that de-qi acupuncture triggers the neuroendocrine network to alleviate pain, but the mechanisms are not clear(22). In our study, we used HRV as an outcome measure, to check whether the acupuncture effect was correlated to autonomic change. HRV has long been recognized as a noninvasive indicator of autonomic nervous system activity(20, 33). Indeed, HRV coherence is related to many physiological benefits, including short-term improvement in cardiovascular and respiratory function, and an increase in vagal afferent activity, which converses pain signals and sympathetic outflow, and thereby promotes temporal synchronization of the body(34, 35). Accordingly, the improvement in autonomic dysfunction corresponds with the balance of yin/yang and implies the adjustment of neuroendocrine in the body microenvironment(20). In this study, we noted that acupuncture has only a short-term effect in adjusting the autonomic dysfunction within the acupuncture group; the benefit did not meaningfully outweigh that received by the medication (control) group (p>0.05). Nevertheless, inter-group analysis revealed that subjects in the high-dose group had greater HRV change, a result which can be interpreted two ways. First, the effect of acupuncture on the autonomic system is short-term rather than long-term. Second, the stimulation of more acupoints may lead to more change in HRV activity, but not greater efficacy in pain relief or symptom control. The mechanism by which acupuncture relieves dysmenorrhea may not directly derive from a change in autonomic nervous activity. We therefore wonder whether the effect of acupuncture in dysmenorrhea is correlated with alterations in serum cytokines, such prostaglandin E and prostaglandin F2 alpha, as has been revealed in previous literature(36). Further study to evaluate the role of serum cytokines is encouraged.

Potential mechanisms of pain reduction

The mechanism of pain associated with dysmenorrhea can be addressed in two aspects: the neuro-endocrine regulated and the neuro-physiologic related. As our study indicates that subjects who adopt acupuncture could use less analgesics, we suppose that acupuncture may have some neuro-endocrine effect(37, 38). In this regard, a previous study noted that acupuncture could have both an anti-inflammatory and an analgesic effect, which might be associated with its inhibition of spinal p38MAPK activation(39) or its regulation of serum prostaglandin E2 or F2 alpha(40). Because patients who used acupuncture required less NSAIDs, acupuncture may have a similar anti-inflammatory effect as NSAIDs, but without the side effects of gastrointestinal discomfort or ulcer stimulation.

On the other hand, some studies have noted that the shift in the estradiol/progesterone ratio in favor of estradiol seems to be the pathogenic principle behind dysmenorrhea(41, 42). We therefore suppose that acupuncture might somehow affect the related hormone balance. In animal models, acupuncture had been noted to regulate neuroendocrine activity and the related receptor expression of the hypothalamus-pituitary-ovary (HPO) axis(38, 43). Clinically, some gynecologist also use oral contraceptives or progestins (OCT) for primary dysmenorrhea(44). If acupuncture could adjust the HPO axis and thereby relieve the related symptoms, then patients can avoid taking OCTs which might have unwanted side effects such as increased risk of endometriosis, blood clot, stroke or cancer(45).

Holistic effect of acupuncture on dysmenorrhea

The results indicate that acupuncture could reduce subjects' dependence on analgesics and improve their VAS and VMSS scores, which means increasing their ability to work and allowing them to resume more normal activity with fewer symptoms. Compared to the alternatives, acupuncture has fewer side effects and is more cost-effective, especially considering that the number of acupoints is not linearly related to outcomes.

Limitations

We noted some bias and limitations regarding the study. The first is that the size of the study could me more to be more powerful. Second, there is as yet no consensus on the optimal acupuncture schedule for any individual disease. We designed the schedule based on the Traditional Chinese Medicine meridian theory, but others might select different acupoints and devise a different schedule when treating the same condition.

Conclusions

We conclude that acupuncture can mitigate dysmenorrhea in terms of providing pain relief, reducing analgesic dependence, improving symptoms and improving quality of life. Furthermore, treatment efficacy is not directly proportional to the dose or number of acupoints stimulated. A well-designed acupuncture schedule with de-qi maneuver is probably more important than the number of needles. We thus concluded that the effect of acupuncture in dysmenorrhea is not direct correlated with the autonomic nervous system adjustment. Acupuncture might have a short-term effect in changing the HRV parameters, yet the true mechanism for acupuncture in dysmenorrhea still warrants further investigation.

Abbreviations

SF-12
12-Item Short Form Health Survey; HRV:Heart rate variation; HF:High frequency; HPO:Hypothalamus-pituitary-ovary; LF:Low frequency; NSAIDs:Non-Steroidal Anti-Inflammatory Drugs; OCT:Oral contraceptive pills; R-MSSD:root-mean square of differences of successive RR intervals; SDNN:standard deviation of adjacent peak-to-peak (NN) intervals; TP:Total power; VMSS:Verbal Multidimensional Scoring System; VAS:Visual Analog Scale; VLF:Very low frequency.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and materials

The datasets used for the current study are available upon reasonable request from the corresponding author.

Competing Interests

The authors declare that they have no competing interests.

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Author's contributions

1. Tsai-Ju Chien*, MD.MA.MS.PhD: Study Design and conception; Drafting of the manuscript
2. Yi-Shuo Huang MD: Acquisition of data
3. Chun-Yu Kuo MS; Analysis and interpretation of data; statistical analysis
4. Yu Ching Cho MD: Acquisition of data
5. Hsin Yu Chen MD: Acquisition of data
6. Chi-Chang Chu MD: Acquisition of data
7. Ting-Yu Cheng MS: literature research

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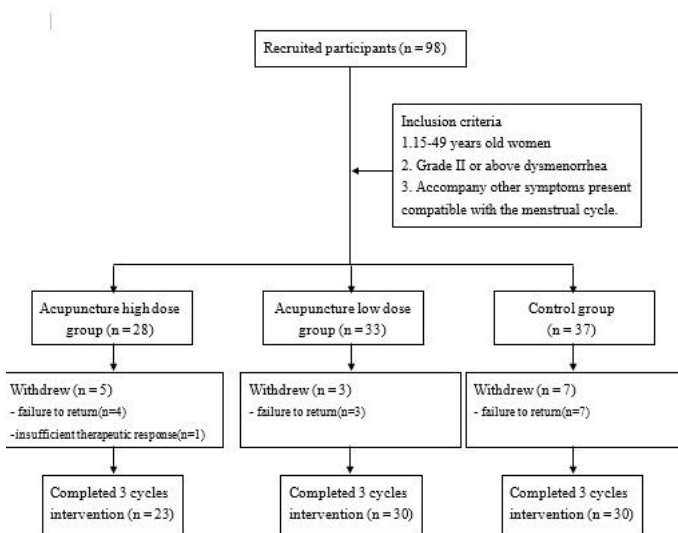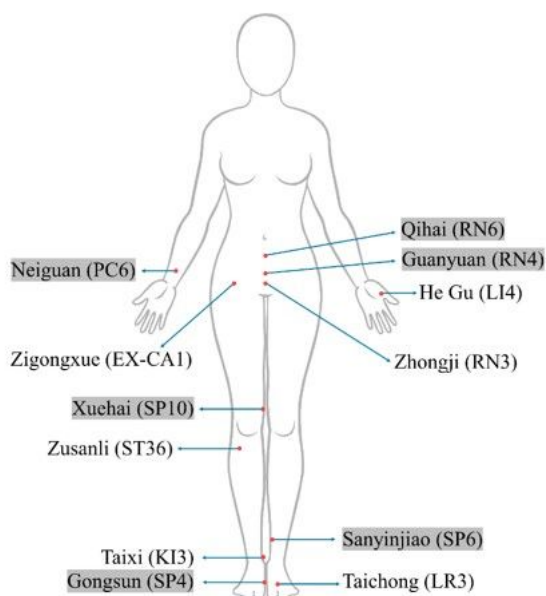
Figures

Figure 1

Flow chart of study

Acupoint	Location
RN6	On the anterior median line of the lower abdomen, 1.5 cun below the umbilicus.
RN4	3 cun below the umbilicus, on the midline of the abdomen.
SP4	On the medial aspect of the foot, in the depression distal and inferior to the base of the first metatarsal bone.
SP6	On the medial aspect of the lower leg, 3 cun above the medial malleolus, on the posterior border of the medial aspect of the tibia.
SP10	When the knee is flexed, on the medial aspect of the thigh, the point is 2 cun above the mediosuperior border of the patella, on the bulge of the medial portion of m. quadriceps femoris.
PC6	On the palmar side of the wrist two inches above the transverse crease of the wrist, between the tendons of palmaris longus and flexor carpi radialis.
LI4	On the highest spot of the muscle when the thumb and index fingers are brought close together.
RN3	4 cun below the umbilicus on the mid-line.
LR3	Just distal to the junction of the bases of the 1st and 2nd metatarsals.
KI3	On the medial aspect of the foot, posterior to the medial malleolus, in the depression between the tip of the medial malleolus and tendo calcaneus.
ST36	On the anterior aspect of the lower leg, one finger-breadth (middle finger) from the anterior crest of the tibia.
EX-CA1	3 cun lateral to the anterior midline and 1 cun superior to the upper border of the pubic symphysis.

Figure 2

Selected acupoints in the study high dose acupuncture group: All acupoints low dose acupuncture group▯gray-colored mark: PC6, SP4, SP6, SP10, RN4,RN6

Supplementary Files

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