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Abstract

Background and aims: Exercise-induced hypoalgesia (EIH) is a well-established phenomenon in pain-free individuals that describes a decrease in pain sensitivity after an acute bout of exercise. The EIH response has been demonstrated to be sub-optimal in the presence of persisting pain. Menstrual pain is a common recurrent painful problem with many women experiencing high levels of pain each cycle. However, the EIH response has not been examined in a cohort of women with high levels of menstrual pain. This research aimed to examine whether EIH manifests differently in women with varying levels of menstrual pain. The primary hypothesis was that women with high levels of menstrual pain would demonstrate compromised EIH. Secondary aims were to explore relationships between EIH and emotional state, sleep quality, body mass index (BMI) or physical activity levels.

Methods: Pressure pain thresholds (PPT) were measured in 64 participants using a digital handheld algometer before and after a submaximal isometric-handgrip exercise. EIH index was compared between low (VAS 0–3), moderate (VAS 4–7) and high (VAS 8–10) pain groups, using a linear mixed model analysis with participant as a random effect, and site, menstrual pain category and the interaction between the two, as fixed effects.

Results: EIH was consistently induced in all groups. However, there was no statistically significant difference between the pain groups for EIH index ($p = 0.835$) or for any co-variates ($p > 0.05$).

Conclusions: EIH was not found to differ between women who report regular low, moderate or high levels of menstrual pain, when measured at a point in their menstrual cycle when they are pain free.

Implications: This study provides insight that EIH does not vary in women with differing levels of menstrual pain when they are not currently experiencing pain. The current findings indicate that, although menstrual pain can involve regular episodes of high pain levels, it may not be associated with the same central nervous system dysfunctions as seen in sustained chronic pain conditions.

Keywords: exercise-induced hypoalgesia; dysmenorrhea; menstrual pain; endogenous analgesia.

1 Introduction

Primary dysmenorrhea (menstrual pain) is characterised by recurrently painful menstruation in the absence of an underlying pelvic pathology [1–4]. Its prevalence is high, with between 21% and 26% of menstruating women experiencing severe menstrual pain [4]. The condition is also reportedly associated with sleep disruption [5] and reduced quality of life [6]. There is also significant economic burden associated with high levels of menstrual pain resulting from absenteeism and reduced productivity [7] and a two to three-fold increase in healthcare costs [8]. Despite the high prevalence and the significant impact on women, this condition is largely overlooked in the persistent pain literature.

Factors increasing the risk of primary dysmenorrhea include family history, increased stress, extremes of body weight (significantly underweight or obese), and tobacco

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use [1, 9]. Ju et al. [10] found that less painful menstruation was associated with increasing age, parity, a healthy body mass index (BMI), and oral contraception use.

Exercise-induced hypoalgesia (EIH) describes the phenomenon of reduced sensitivity to noxious stimuli following a bout of exercise. It is characterised by an increase in pain threshold and a reduction in pain intensity rating during and following exercise [11]. Whilst there is debate regarding the exact pathway by which EIH operates it is consistently reported in healthy populations, and is thought to represent a normally functioning endogenous analgesic system [12]. The EIH response is reportedly influenced by factors such as gender [13, 14] and activity levels [15, 16]. Furthermore, studies in healthy individuals have demonstrated an EIH response at both local [17, 18] and remote [18, 19] assessment sites. Both isometric contraction exercises and aerobic exercise have been shown to produce a robust EIH response [16, 17, 20, 21]. EIH response seems to be dosage-dependent, with submaximal, long duration isometric contraction exercise proving particularly efficacious [19, 20].

It has been reported that multimodal pain hypersensitivity is present throughout the menstrual cycle in dysmenhorreic women [2–4], perhaps indicating a dysfunctional endogenous analgesic system.

This study therefore sought to investigate the effectiveness of the EIH response in women with low, medium or high levels of menstrual pain. A secondary aim was to explore potential relationships between EIH and emotional state, sleep quality, BMI, oral contraceptive use, age, age at menarche and activity levels in these groups. It was hypothesised that EIH response would be lower in women with higher levels of menstrual pain.

2 Materials and methods

2.1 Participants

A single-blinded, within-subject experimental design was used. Sixty-nine female volunteers were recruited by advertisement and word of mouth from Curtin University (Western Australia) and from the local community. Eligible participants had to be aged between 18 and 35 years, have a regular menstrual cycle (28–32 days), and be nulliparous. Participants were excluded if they had any known pelvic pathology (e.g. endometriosis), were pregnant, had any musculoskeletal conditions (e.g. fibromyalgia) or a systemic disease potentially affecting their sensory system. A decision was a-priori made to categorise participants into three pain groups according to visual analogue scale (VAS) pain scores reported for menstrual pain. Pain groups were defined based on a previous study by Slater et al. [4] with low pain (VAS 0–3), moderate pain (VAS 4–7) and high pain (VAS >7). This was performed after data was collected to ensure blinding of the assessors.

Written informed consent was obtained from all participants prior to inclusion in the study. The study was approved by the Human Research Ethics Committee of Curtin University (HRE2017-0544), and adhered to the Declaration of Helsinski.

2.2 Questionnaires

In addition to providing demographic information, participants completed a set of questionnaires prior to testing. These included: an initial questionnaire involving items about menstrual history and including a numeric rating scale from 0 to 10 (0 representing “no pain” and 10 representing the “worst possible pain”) used to rate a participant’s worst pain commonly experienced during their menstrual cycle; the 21-item Depression, Anxiety, Stress Scale (DASS-21); the International Physical Activity Questionnaire (IPAQ); and the Pittsburgh Sleep Quality Index assessment (PSQI). Completed questionnaires were sealed in an envelope and responses de-identified.

2.3 Depression, anxiety and stress

The DASS-21 measured whether self-reported negative emotional states of depression, anxiety and stress had affected the participant in the previous week [22]. Previous studies have demonstrated correlations between high stress levels and primary dysmenorrhea, depression and exacerbated pain responses, low mood and a reduced EIH response [10, 23].

2.4 Physical activity

The short-form IPAQ was used to measure participants’ level of physical activity over the previous 7 days. The questionnaire estimates the level of physical activity in the four areas of work, leisure, transportation and household activities [24]. Physical activity levels have been demonstrated not to be correlated with EIH in a group of male

and female adolescents [16]. More recently, it has been demonstrated that physical activity level has no influence on EIH after a prolonged gripping exercise in healthy college-age women [25]. However, this has not been explored in the context of menstrual pain levels.

2.5 Sleep quality

Since poor sleep quality has been observed in women with severe menstrual pain [5], the PSQI was used to measure sleep quality and pattern in the previous month. The questionnaire consists of 19 items, with a lower score indicating a higher quality of sleep [26].

3 Procedure

3.1 Pre-test intra-rater reliability

Prior to study commencement, the assessors (SY, CC, ET, JN, RL) were formally trained in subject instruction and pressure algometer application for a total of 3 h over three occasions [27]. This included standardising their rate of pressure application, accurate land-marking of test sites, and applying pressure perpendicular to the skin. Following this, a pilot study was conducted where each assessor randomly measured pressure pain thresholds (PPT) of 10 participants at the specific sites for the present study (tibialis anterior/forearm). The intra-rater reliability was excellent (all tester's ICC = 0.94–0.96).

3.2 Test session

Following familiarisation to PPT measurement at the anterior thigh, the testing sites were randomly allocated via a balanced block-randomisation procedure. PPT was assessed at both local (forearm) and remote (tibialis anterior) sites, following the procedure described below. After a quiet 5-min rest session, PPT was assessed again at both sites. This provided within-participant test-retest values (control condition). Following another 5-min rest, pre-exercise baseline PPT measurements were taken at the same test sites. A final set of PPT measurements were taken immediately after the exercise session. Figure 1 illustrates the testing protocol.

Each participant was seated on a chair and PPT assessments completed by two assessors. One assessor was responsible for performing PPT assessment, while the second assessor recorded values on a data collection sheet to blind the first assessor to PPT values. The participant was instructed not to disclose any questionnaire information, in particular their menstrual pain levels, to the assessor in order to ensure blinding to pain group. All test sessions lasted approximately 30 min.

3.3 Assessment of pressure pain thresholds

PPT were assessed using a handheld digital pressure algometer (Somedic AB, Sweden) with the 1.0 cm^2 probe held perpendicular to the skin, pressure increased at 40 kPa/s. A pen was used to mark the local site on the participant's dominant forearm (ventral forearm approximately 8 cm distal to the biceps tendon) and the distant site at the participant's contralateral tibialis anterior (8 cm above ankle joint line, 1 cm lateral to tibial crest). The order of testing at the two sites was randomised. A standard script of instructions was read to each participant in accordance with Waller et al. [27], with the participant asked to press the handheld button as soon as the sensation changed from pressure to uncomfortable to painful pressure. Since a total of four sets of measurements were taken at each site in a relatively short time-frame, only two repetitions were completed at each site and the average was extracted for analysis.

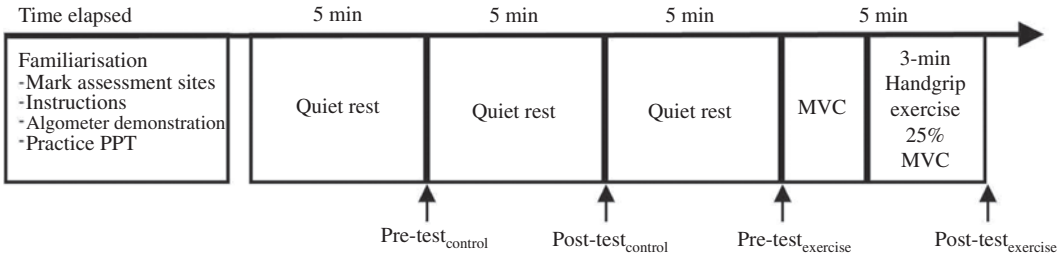

Fig. 1: An illustration of the procedures taken during test session performed on each participant. The sequence of pressure pain threshold assessments at the forearm and lower leg were randomised. MVC = Maximal voluntary contraction.

3.4 Submaximal isometric contraction exercise

The submaximal, long duration isometric contraction exercise involved sustained grip using a hydraulic handheld dynamometer (Jamar; Sammons Preston, Rolyon, Bolingbrook, IL). The participant held the dynamometer in their dominant hand, while sitting in a chair, shoulder slightly abducted so that the elbow was supported on a desk surface. The participants were positioned so that they could see the dynamometer dial in a screen at all times. To measure maximum voluntary contraction (MVC), the participant was instructed to squeeze the dynamometer as hard as possible. Twenty-five percent of this MVC value was then calculated and the participant was instructed to squeeze the dynamometer and sustain this 25% MVC value for 3 min or until voluntary fatigue. Fatigue was defined as the point where the participant was unable to maintain their 25% MVC despite verbal encouragement. The participant received visual feedback from the dynamometer dial, and verbal encouragement from the assessor to maintain their 25% MVC value.

3.5 Power calculation

A power analysis using G Power 3.1.9.2 (Heinrich Heine University, Dusseldorf Germany) was used to estimate the sample size needed for detecting a "session" × "group" interaction for EIH in a mixed model design. With the significance level set at $p < 0.05$, a 0.5 correlation among repeated measures, and the effect size for differences between groups estimated to be small, it was determined that a total of 18 per group (three groups) would yield a power of 0.90.

3.6 Data analysis

Data were analysed using Stata V15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). The primary aim of this study was to determine if a difference in EIH response was demonstrated between the menstrual pain groups. An EIH index (measured in kPa) was calculated as the measure of EIH response using the method of Naugle et al. [19]: EIH index = (Post-test $PPT_{exercise}$ – Pre-test $PPT_{exercise}$) – (Post-test $PPT_{control}$ – Pre-test $PPT_{control}$). A positive EIH index value is indicative of reduced pain sensitivity after exercise [19].

Linear models were used to assess whether continuous covariates differed between pain category groups. Chi-square tests with Fisher's exact p-values were used for categorical covariates. A linear mixed model was used to investigate the effect of menstrual pain group on EIH index, including participant as a random effect, and site (forearm/tibialis anterior), menstrual pain category (low, moderate or high) and the interaction between the two, as fixed effects. This model was fitted again including each covariate individually, in order to see whether any observed effects were altered after controlling for these factors. Univariate associations between covariates and EIH index were also considered using linear models.

4 Results

Sixty-nine participants completed the experiment. Of these, five participants were excluded due to reports of an irregular menstrual cycle ($n = 2$), or musculoskeletal pain ($n = 3$) on their initial questionnaires. Thus, data from 64 participants are presented here, categorised into the three pain groups as follows: low pain (VAS 0–3) $n = 25$, moderate pain (VAS 4–7) $n = 21$ and high pain (VAS 8–10) $n = 18$.

4.1 Demographic and participant characteristics

The participants' profiles for each pain group are presented in Table 1. None of these characteristics differed between menstrual pain categories (all $p > 0.05$).

4.2 EIH index and menstrual pain group

Figure 2 shows the mean EIH index at both the local and remote sites for the three pain groups. EIH was produced when calculated for all subjects and including both sites [mean = 38.8, 95% CI (24.2–53.4)]. The EIH effect size (Cohen's d) for the local site was 0.29 and the remote site was 0.16. The mean EIH index did not differ between the pain categories (χ^2 (2) = 0.36, $p = 0.835$), or between sites (χ^2 (1) = 1.05, $p = 0.307$), nor was the interaction between these two factors significant (χ^2 (2) = 0.12, $p = 0.942$). No association was found between any of the covariates and EIH index (see Table 2). Mean PPT scores for each group are provided in the Supplementary Material.

Table 1: Participants' demographic and personal characteristics by menstrual pain category [mean (sd) unless otherwise noted].

Covariates	Menstrual pain category			Test statistic[a]	*p*-Value
	Low ($n=25$)	Mod ($n=21$)	High ($n=18$)		
Age (years)	26.6 (5.0)	25.6 (4.8)	26.2 (3.9)	$\chi^2(2)=0.51$	0.777
BMI (kg/m^2)	21.7 (4.4)	22.0 (4.3)	23.1 (5.1)	$\chi^2(2)=1.02$	0.601
Age at menarche[b]	12.5 (1.3)	11.8 (1.5)	12.4 (1.2)	$\chi^2(2)=3.45$	0.178
IPAQ METmins	1806 (1779)	2175 (1846)	1994 (3610)	$\chi^2(2)=0.27$	0.873
PSQI	4.1 (2.0)	4.1 (1.7)	4.7 (2.7)	$\chi^2(2)=0.92$	0.631
DASS					
Depression	2.5 (2.4)	3.0 (1.9)	2.8 (3.1)	$\chi^2(2)=0.64$	0.728
Anxiety	2.3 (2.7)	2.4 (2.4)	2.7 (1.9)	$\chi^2(2)=0.32$	0.854
Stress	4.2 (3.8)	4.6 (2.7)	3.7 (3.2)	$\chi^2(2)=0.75$	0.687
Contraceptive pill *n* (%)	3 (12)	1 (4.8)	3 (16.7)	$\chi^2(2)=1.46$	0.469
IPAQ					
Low	10	5	7	$\chi^2(4)=3.54$	0.511
Mod	8	6	7		
High	7	10	4		

[a]The test statistic (and *p*-value) is for the effect of period pain group on each covariate.
[b]Data only available for $n=20$ of moderate pain group.
BMI = Body mass index; IPAQ = International Physical Activity Questionnaire; METmins = METmins are multiples of the resting metabolic rate multiplied by minutes performed; DASS = Depression and Anxiety Symptoms Scale.

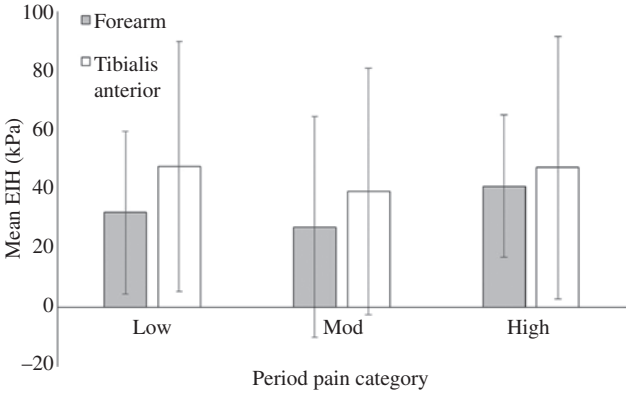

Fig. 2: Mean (SD) EIH index across all pain groups (low, moderate, high) for the local and remote test sites (forearm and tibialis anterior, respectively). Error bars represent the 95% confidence intervals for the mean.

Table 2: β Coefficients for the association between the covariates and EIH index.

Covariates	β Coefficient[a] (95% CI)	Z statistic	*p*-Value
Age (years)	−0.7 (−3.8 to 2.4)	−0.43	0.670
BMI (kg/m^2)	−1.0 (−4.2 to 2.1)	−0.64	0.521
Age at menarche[b]	−1.7 (−12.7 to 9.3)	−0.31	0.759
IPAQ MET	−0.0005 (−0.006 to 0.005)	−0.17	0.864
PSQI	3.9 (−2.8 to 10.6)	1.14	0.252
DASS			
Depression	4.7 (−1.1 to 10.4)	1.59	0.113
Anxiety	2.6 (−3.3 to 8.6)	0.86	0.387
Stress	3.1 (−1.2 to 7.4)	1.42	0.155
Contraceptive pill (Ref = no)	−13.5 (−58.9 to 31.9)	−0.58	0.560
IPAQ			
Low	Ref		
Mod	26.1 (−8.0 to 60.1)	1.5	0.133
High	16.0 (−18.0 to 50.0)	0.92	0.357

[a]For continuous covariates (e.g. age, BMI, DASS subscales), the β coefficient is interpreted as the change in mean EIH index by increasing one unit in the covariate. For categorical covariates (taking contraceptive pill and IPAQ) the β coefficient is the change in mean EIH index in comparison to the reference category.
[b]Data only available for $n=20$ of moderate pain group.

5 Discussion

The purpose of this study was to evaluate the EIH phenomenon in women with varying levels of menstrual pain. To our knowledge, this is the first study to investigate such a relationship. Our results demonstrated that EIH was induced at both the local and remote test sites across all participants, with no statistically significant differences in EIH response between menstrual pain groups.

The findings of the current study, suggest that the exercise was effective at inducing the EIH response [11]. However, the lack of difference in EIH response between groups with varying levels of menstrual pain was unexpected. Impaired EIH has been demonstrated in multiple populations who experience frequent and/or persisting pain [28–32]. The current findings seem to indicate that repeated, cyclical bouts of high menstrual pain are not related to alterations in endogenous analgesic responses

as represented by a compromised EIH response. Few other studies have investigated endogenous analgesia in an episodic pain condition and so there is little data with which to compare these results. It has been demonstrated that endogenous analgesia is dysfunctional in individuals with frequent episodic headaches [33]. However, Drummond and Knudsen [33] used conditioned pain modulation (CPM) rather than EIH to evaluate endogenous analgesia and there is still debate in the literature about whether CPM and EIH are correlated [12, 18, 34, 35].

The present study utilised an established isometric hand-grip protocol to explore the EIH between women with different levels of menstrual pain. The choice of exercise protocol was governed by supporting evidence which demonstrates consistent and robust EIH after with submaximal, long duration isometric contraction [19, 20], availability of resources and considerations regarding the burden on participants. However, there are other exercise protocols which have been demonstrated to produce and EIH response such as high intensity aerobic exercise [12, 36]. In fact, there is data suggesting that vigorous aerobic exercise may produce a larger EIH response than isometric exercise in younger populations (19–30 years) [19]. It is possible that differences in the extent of the EIH response between the different modes of exercise is that they operate by different mechanisms [12]. Therefore, given the potential for a larger EIH response or the potential to explore slightly different mechanisms future research could explore EIH using both isomeric and vigorous aerobic exercise in a similar cohort. However, a limitation of such an approach would be increased resources required and increased participant burden.

Slater et al. [4] explored the relationship between pain hypersensitivity, as measured with quantitative sensory testing, and menstrual pain levels, finding a strong relationship between higher levels of menstrual pain and widespread cold and pressure hyperalgesia. It is still unclear as to whether impaired endogenous analgesia, as reflected by dysfunctional CPM or EIH, and sensory hyperalgesia involve the same central nervous system mechanisms, although an association between degree of widespread hyperalgesia and CPM have been shown in patients with fibromyalgia [37]. The current findings seem to indicate that, although menstrual pain involves regular episodes of high pain levels, the condition may not be associated with the same central nervous system dysfunctions as seen in sustained chronic pain conditions such as fibromyalgia [29–31] or whiplash associated disorder [32].

Previous studies have shown associations between menstrual pain severity and factors such as age, age at menarche, BMI, sleep quality, and physical activity levels [9, 10, 38]. However, our study did not demonstrate any association between menstrual pain group and any of these co-variates. One explanation for this might be that our study was powered for an EIH response and therefore, was likely underpowered in respect to this secondary analysis. Hence, the lack of correlation should be considered with caution.

6 Limitations, methodologic considerations and future research

Given the repeated nature of the PPT testing there was the potential to make the participants more sensitive to subsequent tests. Repeatedly applying the algometer to the same test site in quick succession may cause the participant to become sensitised to the testing. To minimise this, test sites were randomised in order limit repeated consecutive application of the algometer at the same site. Furthermore participants were provided with a 5 min interval of quiet rest between the control and exercise session.

In the present study, the low period pain group were defined as those reporting menstrual pain in the range of 0–3 out of 10. Thus, it cannot be ruled out that EIH may behave differently between a cohort of women who experience no menstrual pain and those who experience this episodic and cyclical pain. It is a recommendation for future research to include a no menstrual pain group to explore whether this issue.

Participants experiencing menstrual pain at the time of testing were excluded in order to reduce hormonal covariates and to mitigate the potential confounding effect of current pain. However, there may be value in a further study, with data collections occurring both when the participant is pain-free and when they are experiencing their menstrual pain.

Finally, parallels have been drawn between the ability to reduce pain sensitivity via exercise or by using a conditioning painful stimulus [21]. Future studies may consider studying CPM in conjunction with EIH in this cohort. EIH together with CPM may reflect a more complete picture of the functioning of the endogenous analgesic system in this population.

7 Conclusions

A prolonged, submaximal, isometric contraction handgrip exercise was sufficient in inducing EIH in a cohort of women with varying levels of menstrual pain. EIH was demonstrated both at a site local to and remote from the

arm being exercised. However, contrary to expectations, EIH response was not found to differ between high, moderate and low menstrual pain groups.

Authors' statements
Research funding: None declared.
Conflict of interest: None declared.
Informed consent: Written informed consent was obtained from all participants prior to inclusion in the study.
Ethical approval: The study was approved by the Human Research Ethics Committee of Curtin University (HRE2017-0544), and adhered to the Declaration of Helsinski.

Author contributions

All authors contributed to design of the study. SY, CC, JN, ET and RL completed data collection, data entry and contributed to drafting the article. DH performed the statistical analyses, with contributions from MT. All authors contributed to interpreting the results, commenting on the manuscript, critically revising the article, evaluating intellectual content and gave final approval of the manuscript.

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