Pilot Study: Assessing the Efficacy of the Supplementation of 'Period Bites' on Primary Dysmenorrhea in Women Aged From 18-25 Years

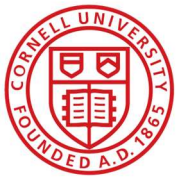
Armita A. Jamshidi

Supervised by Dr. Marla Lujan

College of Arts and Sciences, Cornell University

Laidlaw Leadership and Research Scholar's Program

August 2022



Cornell University

With funding from the Epperson Entrepreneurship Fund, the Dan Cane Entrepreneurial Scholars Program, and the Contribution Project

Contents

Executive Summary

Primary dysmenorrhea (PD) is a gynecological condition defined by a cramping pain in the lower abdomen in the absence of a pelvic pathology. Its prevalence ranges between 25% and 90% in various studies observing the disorder in adolescent females (Direkvand-Moghadam & Khosravi 2012a). During menstruation, after endometrial cells in the lining of the uterus start to break down, women release molecular compounds, called prostaglandins. These compounds stimulate the uterus to contract, the cervix to thin, and the release of the hormone vasopressin, which can lead to symptoms of PD, including period cramps and/or menstrual pain (Direkvand-Moghadam & Khosravi 2012a).

Currently, management strategies for the disorder fit in two categories, each with their own issues: on one end, pharmacological solutions such as hormonal contraception and analgesics rectify the root cause of PD. While these compounds have some degree of effectiveness to alleviate PD symptoms, they do not do so naturally, as demonstrated through the constant need to acquire artificial compounds. Further, these types of agents can be demanding to the consumer because they require them to regularly monitor their usage, and thus are inconvenient and unsustainable for long-term use. For example, birth control must be taken once per day, at or around the same time: this only further demonstrates its inconvenience to the consumer (Coco 1999). On the other end, non-pharmacological options to alleviate PD symptoms include heating and massage pads, heating therapy, and over the counter creams. However, because these solutions alleviate pain from the outside, there once again lies the problem of inconvenience, as these approaches cannot always be readily employed given the individual's usual life activities (e.g., wearing a heating pad on the way to work, but not being able to wear it at work). Furthermore, because oral contraceptive pills and anti-inflammatory

medications (NSAIDs) are chemical drugs and have possible side effects, consumers are now looking for alternative natural, herbal treatments (Direkvand-Moghadam & Khosravi 2012a). Therefore, because most solutions for PD pain prove to be inconvenient or undesirable, there currently lies a gap in solutions for PD pain on the market.

In order to mitigate the lack of information in this area, researchers continually explore primary dysmenorrhea (PD) to examine how factors – including, but not limited to sleep, diet, and exercise – might affect its symptoms. By understanding how these elements attribute to the complexity of the pervasive disorder, researchers might be able to target the root cause of PD and develop more suitable, convenient solutions that are sustainable for long-term use. Through giving women nutraceuticals for PD and observing its effect on their period cramps, we will explore solutions to alleviate the symptoms of the disorder more efficiently. Existing research has provided evidence for how different foods could alleviate symptoms of PD. We hope to leverage those ingredients to offer a more sustainable and convenient solutions to women with PD. We will conduct a pilot study to examine the effect of a 'period snack' – classified by a mixture of supplements known to help with period pain – on the period cramps of women aged 18-25 years. This will be done through randomly assigning half of the participants the period snack and the other half a placebo. These snacks will be consumed over the course of five days, starting two days before the participants' next menstrual cycle, and extending three days into the cycle. We hypothesize that the period snack will help alleviate congestive symptoms of PD, and have a no effect on spasmodic symptoms of PD.

We will use this pilot study to assess the feasibility of the intervention and generate the preliminary data needed to identify an accurate number of participants needed to demonstrate statistical significance of the period snack on PD symptoms using our measurement tools. As

well, we will qualitatively observe how the snack influences congestive PD versus spasmodic PD. Lastly, this pilot study will help us to understand any gaps in our protocol so we can effectively limit confounding variables in a proceeding and adequately powered study. Ultimately, these results will help set the stage for determining the effectiveness of the period snack in alleviating symptoms of primary dysmenorrhea.

Introduction

Dysmenorrhea is one of the most prevalent disorders affecting women of all gynecological age. One study finds that the pervasiveness ranges between 50 percent and 91 percent for women between the ages of 37 and 39 (Negriff et. al 2009). *The American Society of Pain Management Nurses* classifies primary dysmenorrhea as painful menstruation that occurs without any underlying gynecological disease (Habibi et. al 2015). There are two types of primary dysmenorrhea with unique symptoms. Congestive symptoms of PD commence before menses, and the Menstrual Symptom Questionnaire (MSQ) describes it as a "heavy", "dull", "aching pain in the lower abdomen", while spasmodic PD symptoms occur at the time of menses, and the MSQ describes it as a severe "spasmic" pain (Chesney & Tasto 1974). Many women have been found to experience both types of symptoms, and they thus have both disorders (Negriff et. al 2009).

While PD causes painful cramping, aching, constipation, headaches, backaches, and many other side effects, the secondary consequences encompasses the loss of time for women to pursue their day-to-day activities. This absenteeism can range anywhere from less than one hour to several days (<4) each month, according to the Cox Menstrual Symptom Scale (Direkvand-Moghadam & Khosravi 2012a). One study found that the disorder has been identified as the leading cause of school and work absenteeism in adolescents and young adults (Negriff et. al 2009). Much research in this field has tested how specific supplements help with symptoms of primary dysmenorrhea, yet there lies a paucity of knowledge in the distinctions between the effects of supplements on congestive symptoms versus spasmodic symptoms. In this study, we will ask participants to specifically rate the extremity of their congestive PD symptoms and spasmodic PD symptoms separately to analyze the efficacy of the period snack on the two types

of PD pain. Moreover, though the disorder thoroughly pervades the female population globally, there continues to lie several holes in research examining ways to subside the symptoms of this disorder: the gaps in knowledge on this topic spur from social, cultural, political, and economical sectors of society. In this clinical trial, we will test whether a ‘period snack’ – classified by a mixture of ingredients known to help with primary dysmenorrhea – alleviate the participants’ period cramps. Specifically, we will distinguish whether the nutraceutical alleviates congestive symptoms, spasmodic symptoms, or both, overall examining the efficacy of the period snack; in terms of its administrational ease, this solution could potentially offer a more convenient way to alleviate symptoms of PD than current products on the market.

Methods

We are testing the effectiveness of the period snack through providing participants with 5 doses of either the snack or a placebo to consume once per day, starting two days before and extending three days into their next menstrual cycle. There are 12 participants in total: 6 participants were randomly assigned to received five doses of the period snack, and the other 6 received five doses of the placebo snack.

Participants are recruited through filling out an interest form attached to a flyer, which is distributed around Cornell University campus and the wider Ithaca area. Upon demonstrating interest in the study, the participant will be invited to an in-person standardized interview with the researchers in a private classroom. Prior to the interview, the participant is randomly divided into one of two groups: one group receives five doses of the period snack, and the other receives five doses of a similar-sized snack. The assigned snack will be brought to the interview. The goal of the interview is for us to collect information about the participants' health and eligibility, give them the snack they were assigned, and for the participant to ask any questions they may have had about the study. Women between the ages of 18 and 25 who experience PD and have no pathological disorders are included in the study. Exclusion criteria includes the following: pregnant or breast feeding within the past six months; diagnosis of primary or secondary amenorrhea; body mass index less than the 1st percentile or body weight above 300 lbs; prescription for medication causing menstrual suppression; unwillingness to avoid painkillers (NSAIDS) for the duration of the study unless absolutely necessary; allergy or aversion to a list of ingredients encompassing substances in the period snack and placebo. Upon obtaining the participants' informed consent, the researcher will collect information about the participants' medical and menstrual history, paying close attention to their history of PD. Thereafter, the

researcher will verbally ask the participant questions on the MSQ to confirm the participants' experience with PD. We will also use the MSQ to examine which PD symptoms the participant experiences regularly. After completing the MSQ, the participant will receive their assigned snack, and they will not be made aware of whether they will receive the period snack or the placebo snack.

The participants will be instructed to take online pre-consumption and post-consumption questionnaires, prompting them to report the extremity and type of pain they experience prior to and during their next expected menstrual cycle. Prior research has demonstrated that the Visual Analogue Scale (VAS) evaluating systems are able to confirm the efficacy of a treatment for PD (Direkvand-Moghadam & Khosravi 2012b). For this reason, the VAS will be utilized to determine the level of pain the participants are experiencing in their pelvic and abdominal areas before and after consuming their assigned snack.

After the participants' last day of menstruation, a final online questionnaire will be sent to them asking about their experience with the study and about the snack they consumed. This questionnaire will confirm the day(s) the participant experiences period pain and will give them the opportunity to provide their opinions on the snack they consumed.

Potentially confounding factors in the study include the participant's sleep quality and duration and physical activity level. As well, only the participants' general dietary habits will be accounted for, which could vary in practicality over the duration of the study. Results of the MSQ and VAS will be used to help identify the optimal sample size needed to determine whether the period snack holds significant efficacy in a proceeding clinical study: this will be done through a power analysis. The data will be analyzed to examine whether the period snack has a different effect on congestive PD symptoms versus spasmodic PD symptoms. As well, the

logistical aspects of the protocol will be tested in this pilot study in order to make modifications for any potential gaps of the intervention.

Expected Results and Discussion

Expected Results

We anticipate that there will be a noticeable (2.6 ± 0.05 in Mean grades ± SD, defined by the VAS) difference on the VAS scores in the intervention group versus the control group. This is because the period snack is composed of many ingredients and nutrients proven to alleviate symptoms of primary dysmenorrhea (Direkvand-Moghadam & Khosravi 2012a; Harel et al. 1996; Hudson 2007). Due to our intention to potentially market the product, the ingredients for the period snack and the placebo snack will be kept confidential between researchers in the study. We also hypothesize that the period snack will target congestive symptoms of PD, based on qualitative feedback received prior to the study. We will consider both previous studies and the power analysis to determine the sample size needed for a larger study. We plan to use 55 participants: the number of participants models a study with a similar methodological structure, in which women in early adulthood were given a detailed questionnaire about their menstrual symptoms, and then provided with a supplement to assess how their PD symptoms changed. The study contained 42 women, yet our proposed sample size is larger to account for attrition (Harel et al. 1996). We expect that our preliminary data on the effect of period snack on congestive PD pain will reveal the actual number of participants needed to have a statistically significant and clinically meaningful change in PD pain: analysis of prior literature and a power analysis will help with this goal.

Discussion

The focus of the study is to examine a difference in PD pain VAS scores in the control group versus the treatment group, to conduct a power analysis for the study to determine the number of participants needed to demonstrate statistical significance, and to pilot test the methods of the study and modify as needed before conducting a larger, more definitive study. While our protocol was modeled after previous studies—i.e., using the VAS to evaluate the efficacy of a supplement for PD symptoms—previous research supports the need to modify existing protocols before conducting larger clinical trials (Direkvand-Moghadam & Khosravi 2012b). The confounding factors outlined previously were predicted before the start of the study, but here we will confirm which variables should be accounted for in the proceeding study.

Given previous research demonstrated that there are no significant differences in severity of menstrual symptoms for women who take oral contraceptives versus those who do not (Negriff et. al 2009), our study only asked the participants about their contraception use, and it did not factor into the participants' eligibility to participate in the study. However, upon looking at similar studies and learning about the role of contraception in a woman's menstrual cycle, having participants who are all taking contraception or who are all avoiding contraception would be useful in simplifying potential factors in the study (Negriff et. al 2009).

Given the time constraints of the study, it was rather difficult to compare each participants' menstrual pain during the intervention versus their PD symptoms during a regular cycle without the study; because this study only looked one menstrual cycle for each participant, it remained difficult to compare the data without a baseline. A previous study conducted a 4-month treatment period as a double blinded crossover study, and the Cox Menstrual Symptom Questionnaire was conducted prior to the study and each month (Harel et al. 1996). In another

study, women were given either an herbal treatment or Ibuprofen multiple times per day over the course of one menstrual cycle and filled out the VAS after they took their prescribed supplement (Direkvand-Moghadam & Khosravi 2012a). This study demonstrated difficulty not only because there was not a set baseline, but also because the nutraceutical was given to the participants to consume one time per day: this potentially could have been more effective if the participant was prescribed to take the snack multiple times per day when they experience cramps. Especially given the fact that the period snack itself is composed of natural ingredients, it is likely that it takes a higher dosage of snacks to create a statistically significant result on the VAS. In a similar sense, depending on each participants' Body Mass Index (BMI), the absorption rate after consuming the snack could have a wide range of effects. In the future study, this should also be accounted for, as it is a significant confounding factor.

The questionnaires used in the study may have also possessed limitations in understanding all the factors that could affect the participant's PD symptoms. Sleep, stress, nutrition, and physical activity all largely influence the extremity of one's period cramps, and these factors should be accounted for in future studies. Another confounding factor found with the questionnaires is the ability of the participant to pinpoint the location of their PD pain, and to be able to distinguish between spasmodic and congestive PD pain. Descriptions of the two different types were given at the time of the initial interview and on each questionnaire, yet there still lies a chance in the inability to distinguish the two, and this could influence the results of the study. Especially given that many participants in the study suffered from both congestive and spasmodic symptoms, distinguishing between the two types of pain could be very challenging. In future studies, focusing on either spasmodic or congestive symptoms of PD, and screening

participants who have one of the two, would better lead the research towards a more direct conclusion.

Thus, though studies similar to our clinical trial played an important role in the protocol and structure, further modifications should be made to limit the confounding variables in future studies. These modifications regard the eligibility and screening of the participants, the questions posed to the participants, and the structure of the protocol for the study. Moreover, these changes will allow for a more accurate and efficient study that will further progress the knowledge surrounding the relationship between nutraceuticals and PD pain.

Conclusion

Primary dysmenorrhea is a disorder that thoroughly pervades the female population around the world, and it is currently the leading cause of school and work absenteeism in adolescents and young adults (Negriff et. al 2009). Through the Laidlaw Leadership and Research Scholar's program, I was able to spend my first summer going through the IRB process and begin the conduct of a pilot clinical trial examining the efficacy of a period snack on primary dysmenorrhea symptoms in women age 18-25. The product tested in this research could potentially yield an effective nutraceutical for women suffering from period cramps of ages 18 to 25. Another major milestone for the research study was identifying gaps in its protocol that could more effectively account for confounding variables, which is critical for making modifications before proceeding with a larger, more comprehensive study.

Acknowledgments

I am forever grateful to Dr. Marla Lujan, Associate Professor in the Department of Nutritional Sciences, for spearheading my progression as a researcher this summer through acting as my faculty mentor for the program. With Dr. Lujan, I would like to thank all of her graduate students for guiding me through the process of obtaining informed consent from participants, thinking critically about confounding factors in my study, and connecting me with students who could help me with my research this summer: in particular, I would like to thank Faith Carter for all of her help and mentoring.

With the Laidlaw Program, I owe a huge thank you to Ru Liu, my program graduate mentor, who has been remarkably supportive of all my ventures this summer and beyond, and who has also offered advice that I will keep with me moving forward.

As well, thank you to Dr. Robert Karpman and Ms. Andrea Ippolito for offering astounding guidance this summer on how to pursue my business; with that, I would like to also express my appreciation to members of the Epperson Entrepreneurship fund, the Dan Cane Entrepreneurial Scholars Program, and the Contribution Project – this pilot study would not have been possible without their support.

Bibliography

Armita Jamshidi is a rising sophomore in Cornell’s College of Arts and Sciences undecided on her major. Her greatest passion lies in mitigating the discrepancy surrounding research within the field of women’s menstrual health; Armita enjoys looking at menstrual health from physiological, social, cultural, political, and socioeconomical lenses as she continuously tries to untangle the complexity of how women’s health has been regarded in the United States and in countries of other cultures. Though Armita was initially hesitant spending her first college summer back at school, she is so glad she took a risk, as she thoroughly appreciates all the material she learned, friends she made, experiences she had, and adventures she indulged in within the Ithaca community and beyond this summer. While Armita believes there lies a huge emphasis on the second summer abroad in the Laidlaw program, she recognizes the importance of each layer of the Scholar’s program, and how deeply it attributes to her growth as an academic, a learner, and an individual.

References

Chesney, M. A., & Tasto, D. L. (1975). The development of the menstrual symptom questionnaire. *Behaviour research and therapy*, *13*(4), 237–244. https://doi.org/10.1016/0005-7967(75)90028-5

Coco A. S. (1999). Primary dysmenorrhea. *American family physician*, *60*(2), 489–496.

Direkvand-Moghadam, A., & Khosravi, A. (2012a). The impact of a novel herbal Shirazi Thymus Vulgaris on primary dysmenorrhea in comparison to the classical chemical Ibuprofen. *Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences*, *17*(7), 668–670.

Direkvand-Moghadam, A., & Khosravi, A. (2012b). Comparison of Verbal Multidimentional Scoring System (VMS) with Visual Analogue Score (VAS) for evaluating of Shirazi Thymus Vulgaris on menstrual pain. *Journal of pharmaceutical and biomedical sciences.* 2230-7885.

Habibi, N., Huang, M. S., Gan, W. Y., Zulida, R., & Safavi, S. M. (2015). Prevalence of Primary Dysmenorrhea and Factors Associated with Its Intensity Among Undergraduate Students: A Cross-Sectional Study. *Pain management nursing : official journal of the American Society of Pain Management Nurses*, *16*(6), 855–861. https://doi.org/10.1016/j.pmn.2015.07.001

Harel, Z., Biro, F. M., Kottenhahn, R. K., & Rosenthal, S. L. (1996). Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. *American journal of obstetrics and gynecology*, *174*(4), 1335–1338. https://doi.org/10.1016/s0002-9378(96)70681-6

Negriff, S., Dorn, L. D., Hillman, J. B., & Huang, B. (2009). The measurement of menstrual symptoms: factor structure of the menstrual symptom questionnaire in adolescent girls. *Journal of health psychology*, *14*(7), 899–908. https://doi.org/10.1177/1359105309340995