

Research Article

A Comparative Study on the Effect of Acupuncture and Neutral Hip Bath among Young Females with Primary Dysmenorrhea – A Prospective Randomised Trial

Abhijna J¹, Vanitha Shetty²

¹PG Scholar, Department of Clinical Naturopathy, Alva's College of Naturopathy and Yogic Sciences, Moodbidri, Karnataka, India.

²Principal, Alva's College of Naturopathy and Yogic Sciences, Moodbidri, Karnataka, India.

DOI: <https://doi.org/10.24321/2278.2044.202303>

I N F O

Corresponding Author:

Abhijna J, Department of Clinical Naturopathy, Alva's College of Naturopathy and Yogic Sciences, Moodbidri, Karnataka, India.

E-mail Id:

abjaabhijna@gmail.com

Orcid Id:

<https://orcid.org/0000-0001-7610-762X>

How to cite this article:

Abhijna J, Shetty V. A Comparative Study on the Effect of Acupuncture and Neutral Hip Bath among Young Females with Primary Dysmenorrhea - A Prospective Randomised Trial. Chettinad Health City Med J. 2023;12(1):10-16.

Date of Submission: 2022-09-04

Date of Acceptance: 2023-02-04

A B S T R A C T

Introduction: Dysmenorrhea is a common medical condition characterised by severe abdominal pain during menstruation. Dysmenorrhea with no obvious pelvic pathology is referred to as primary dysmenorrhea. Acupuncture and hydrotherapy are non-pharmacological interventions that help in reducing pain without any known adverse effects. The current study was aimed at understanding and comparing the effects of acupuncture with those of neutral hip bath on the symptoms and disability associated with primary dysmenorrhea.

Methodology: In the present prospective randomised controlled trial, 70 females aged 21.54 ± 1.73 years fulfilling the study criteria were selected. Subjects were randomly divided into acupuncture and neutral hip bath groups. They were then assessed by the Visual analogue scale and Menstrual symptom questionnaire, outcomes variables assessed on the baseline, mid (30th day) and post (60th day) status of the intervention.

Results: In the present study, analysis of variance (RMANOVA) on Visual analogue scale and Menstrual symptom questionnaire scores yielded significant variation among the conditions. Post hoc Tukey's test showed a significant reduction in mean scores of both acupuncture and neutral hip bath groups. The outcomes variables taken during three intervals, pre vs mid, mid vs post, and pre vs post resulted in a p value ≤ 0.001 , thus, suggesting the equal effectiveness of acupuncture and neutral hip bath in primary dysmenorrhea.

Conclusion: The present study indicates that neutral hip bath was equally effective as acupuncture in the management of primary dysmenorrhea. It reduces the severity of dysmenorrhoeic pain and associated symptoms in young females.

Keywords: Primary Dysmenorrhea, Acupuncture, Neutral Hip Bath, Visual Analogue Scale, Menstrual Symptom Questionnaire

Introduction

Dysmenorrhea indicates painful menstruation. However, the most practical and realistic definition for dysmenorrhea is painful menstruation of adequate magnitude incapacitating everyday activities.¹

Frequently included symptoms such as nausea, sweating, diarrhoea, vomiting, tiredness, and headache occur prior to or during the menses. Its types include primary and secondary dysmenorrhea. Primary dysmenorrhea (PD) is defined as painful menstruation in the absence of pelvic pathology most commonly seen in younger women after the establishment of their ovulatory cycle.² PD is exceedingly common. 50% of menstruating women are reported worldwide with PD, of which 90% of girls are adolescents.³

PD impacts greater than 50% of post-pubescent girls of 18 to 25 years of age with ovulatory cycles, of which, 30-50% go through various ranges of discomfort. The extremely incapacitating pain which interferes with a woman's everyday activities is experienced by about 5-15% of the population. Both the localised and systemic symptoms are results of elevated prostaglandin (PG) levels in the menstrual fluid, resulting in giddiness, vomiting, nausea, backache, fainting, diarrhoea, syncope, giddiness, and uterine cramping.⁴

The health of an adolescent girl also affects the health of the future population.⁵ Dysmenorrhea is regarded as the most common manifestation of all other menstrual complaints and constitutes the greatest burden in developing countries.²

Latest studies suggested that 70.2% of the south Indian population suffer from PD, of which around 50% of girls with dysmenorrhea have to take a leave of absence from colleges or schools. At present, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) appear to have a productive effect in the management of PD but they also have an adverse effect on health.⁶ Thus there is an increased interest towards the use of alternative and complementary therapies.⁷

Although conventional medications provide instant temporary relief in the case of PD, they have associated side effects, drug dependence, and unnecessary medical expenses. Non-medical management includes bed rest, exercise, acupuncture, and herbal medicines.⁸

Naturopathy is one of the traditional healthcare available in India. It is regarded as the science of wholesome living. The naturopathy system of healing is established with the philosophy of natural healing through its own concepts of health, diseases and their management.⁹

Naturopathic management involves many therapies including hydrotherapy, herbal medicine, exercise therapy, nutrition, physical therapy, manipulative therapy, food¹⁰, acupuncture, and traditional Chinese medicine.¹¹

Acupuncture is a Latin word; *acus* means needle and *pungue* means pricking. Acupuncture is a system of treating various diseases of the human body by inserting very fine needles into a particular point of the body to get the desired therapeutic effect.¹²

Acupuncture and acupressure have indicated beneficial aspects in pain, reduction of symptom severity and requirement for analgesics in primary dysmenorrhoea.¹³ A study recommended acupuncture as a mode of treatment for subjects suffering from dysmenorrhea, in particular those subjects for whom oral contraceptives or NSAIDs are refused or contraindicated.¹⁴

The best-known effect produced by acupuncture is the analgesic effect, which is achieved by raising the pain threshold.¹⁵ A study showed that the use of analgesic medication was reduced by 41% in the study group after acupuncture treatment and no change was seen in the other groups.¹⁶

Hydrotherapy was obtained from the Greek word "*hydro*" which means water, and "*therapia*" which means healing. Thus, it is defined as water healing. Hydrotherapy is the therapeutic utilisation of water for positive health benefits. These advantages are due to the thermal and mechanical effects of water interacting with the body. It includes the use of physical properties of water like its specific temperature and pressure to manipulate the flow of blood in the body in order to treat the symptoms of certain diseases.¹⁷

Hip bath (HB) is a treatment in hydrotherapy, in which the lower abdomen, mainly pelvis and genitals including the upper portion of the thigh, is immersed in water which is kept at a particular temperature to gain the desired therapeutic effect.¹⁸

HB is given in various temperatures including cold, hot, neutral or alternate temperatures. For a neutral hip bath (NHB), the temperature of water should be 32° to 36°, and this process involves a duration of 20 minutes.¹⁹ NHB helps to relieve all acute and sub-acute inflammations in the uterus, ovaries, and fallopian tubes, and painful spasms of the vagina and vulva.²⁰ An article published in the Provincial Medical Journal and Retrospect of the Medical Sciences in the year 1843 suggested a warm hip bath for the treatment of dysmenorrhea.²¹

Aim

The study was aimed at understanding the effect of NHB in contrast with acupuncture for alleviating dysmenorrhoeic pain and symptoms associated with PD.

Methodology and Methods

The current study was a prospective randomised controlled trial carried out in the Department of Clinical Naturopathy at Alvas's College of Naturopathy and Yogic Sciences from

February 2022 to April 2022. It involved the screening of over 500 subjects. 70 subjects were finally included in the study after taking informed consent in written format.

The Institutional Ethics Committee's clearance was obtained before the study. It was also registered in CTRI (CTRI Registration number: CTRI/2022/02/040036).

Diagnostic Criteria

The important features included pelvic pain or lower abdominal pain in the absence of radiation to legs and back, initiated mostly after 12 months of menarche. The pain usually appears with the onset of menstrual flow and typically lasts from 8 to 72 hours. Symptoms like diarrhoea, low back pain, nausea, headache, vomiting, and fatigue may also be associated. PD is differentiated from secondary dysmenorrhoea using family history.²²

Inclusion Criteria

Females having dysmenorrhea with ages ranging between 18 and 25 years,⁴ having regular (30 days) menstrual cycles with 4-5 days of bleeding phase, and suffering from PD at least for the past one year were included in the study.

Exclusion Criteria

Females suffering from dysmenorrhoea due to an underlying pelvic pathology (secondary dysmenorrhea),¹ or having a history of taking medication, or a history of abnormal uterine bleeding/ infections were excluded.

Outcome Variables

Visual Analogue Scale

The VAS is represented by a 10 cm line, the sequence corresponding to the opinion of the female with the degree of pain before and after the intervention. As per the scale, the categorisation was as follows: mild: 1-3; moderate: 4-7, and severe: 8-10.²³

Menstrual Symptom Questionnaire

MSQ contains 24 questions, examined as 1 - "never" to 5 - "consistently". This questionnaire consists of 2 divisions with 12 questions with a combination of both congestive and spasmodic factors. Elements in the congestive factor consist of moods or symptoms in the premenstrual phase, and elements in the spasmodic factors consist of symptoms occurring during menstruation like spasms. The range of scores was 12-52 for both congestive and spasmodic factors.²⁴

Intervention

Acupuncture

Subjects were asked to sit in any comfortable position. Needling was done on the points for a duration of 20 minutes as mentioned in Table 1.²⁵

Table 1. Acupuncture Point Name and Needling

Meridian Number	Needling
CV-3	(0.5-1) t-sun, straight
CV-4	(0.5-1) t-sun, straight
CV-12	(1-1.5) t-sun, straight
St-29	(0.5-1) t-sun, straight
UB-23	(0.5-1) t-sun, straight
GV-20	(0.3-1.5) t-sun, posteriorly slanting
Sp-6	(1-1.5) t-sun, straight
Sp-8	(1-1.5) t-sun, straight
K-3	(0.3-1.5) t-sun, straight
St-36	(1-1.5) t-sun, straight

Neutral Hip Bath

The tub was filled with neutral water (temperature – (32-36) °C). Generally, four to six gallons (22.71 litres) of water was sufficient to immerse the hips of the subject up to the naval region in a sitting position. Initially, the subject was asked to drink one-two glasses of cold water and was then asked to sit in the hip bathtub for a duration of 15-20 minutes, and a cold compress was applied to the head. Friction was avoided on the abdomen during the treatment and cold showers and exercises were avoided for a duration of 30 minutes after the bath. The subject was advised to take rest for about 30 minutes.²⁶

Methodology

A total of 70 subjects were selected for the study after applying diagnostic, inclusion, and exclusion criteria. The subjects were randomly divided into two groups [Group A- Acupuncture (n = 35) and Group B - NHB (n = 35)] using a simple lottery method. Baseline assessment was taken initially and then the intervention was started after the bleeding phase/ on the 5th day of menstruation for 10 days. The intervention was again started after 5 days and was given for 10 days, and then mid-assessment was taken before the second cycle/ 30th day of the first intervention. The same protocol was continued for the second month and the post-intervention was after the next cycle/ 60th day of the first intervention.

Statistical Analysis

The data were checked for normal distribution and a two-way repeated-measures analysis of variance was performed. The data were analysed using Repeated Measures Analysis of Variance (RMANOVA) to compare and assess the changes between the groups and across three time points. As the assumption for sphericity was not met, Huynh-Feldt correction was used. Tukey's test for post hoc comparisons

was performed, presented with 95% confidence intervals and considering $p < 0.05$ as significance for all analyses (SPSS Version 19).

Results

The current study was conducted to compare the effect of acupuncture with NHB before, during (in the 1st month) and after (in the 2nd month) the intervention in individuals with PD. The comparison has been shown in Table 2. The effect of Huynh-Feldt correction was analysed (Table 3).

RMANOVA on the VAS scores yielded significant variation among the conditions (Figure 1) $F(1.51, 88.89) = 5.86, p = 0.008$. Post hoc Tukey’s test showed a significant reduction in the mean scores of the acupuncture group in pre vs mid ($p \leq 0.001$), mid vs post ($p \leq 0.001$), and pre vs post ($p \leq 0.001$) analyses, and in those of NHB group, in pre vs mid ($p \leq 0.001$), mid vs post ($p \leq 0.001$), and pre vs post ($p \leq 0.001$) analyses.

0.001) analyses, and in those of NHB group, in pre vs mid ($p \leq 0.001$), mid vs post ($p \leq 0.001$), and pre vs post ($p \leq 0.001$) analyses.

Similarly, RMANOVA on the MSQ scores suggested a significant variation among the conditions (Figure 2) $F(1.24, 72.88) = 4.73, p = 0.026$. Post hoc Tukey’s test showed a significant reduction in the mean scores of the acupuncture group in pre vs mid ($p \leq 0.001$), mid vs post ($p = 0.004$), and pre vs post ($p \leq 0.001$) analyses, and in those of NHB group, in pre vs mid ($p \leq 0.001$), mid vs post ($p \leq 0.001$), and pre vs post ($p \leq 0.001$) analyses.

Tukey’s HSD test for multiple comparisons found that the mean values of VAS, CF, SF, and MSQ were not significantly different between the acupuncture and NHB groups.

Table 2. Group Differences as Suggested by Repeated Measures of Variance

Variables	Acupuncture			Neutral Hip Bath			Between Groups (p Value)
	Pre	Mid	Post	Pre	Mid	Post	
VAS	7.07 ± 1.24	4.45 ± 1.46	2.29 ± 5.1	6.27 ± 1.84	4.43 ± 1.68	2.43 ± 1.91	0.56
CF	42.52 ± 6.87	49.58 ± 5.42	52.61 ± 5.10	41.68 ± 7.18	50.03 ± 5.42	55.37 ± 2.67	0.63
SF	36.77 ± 5.27	26.77 ± 4.92	21.32 ± 4.86	36.47 ± 6.4	24.57 ± 4.70	18.43 ± 3.37	0.09
MSQ	66.52 ± 9.33	49.07 ± 8.9	40.65 ± 9.3	67.3 ± 12.1	46.6 ± 8.64	35.03 ± 4.85	0.23

Table 3. Effects with Huynh-Feldt Correction

Variables	Df	F value	p Value	η^2_p	ω^2
VAS	1.51, 88.89	5.86	0.008	0.090	0.013
CF	1.33, 78.73	6.26	0.009	0.096	0.019
SF	1.26, 75.43	2.44	0.115	0.040	0.007
MSQ	1.24, 72.883	4.73	0.026	0.074	0.016

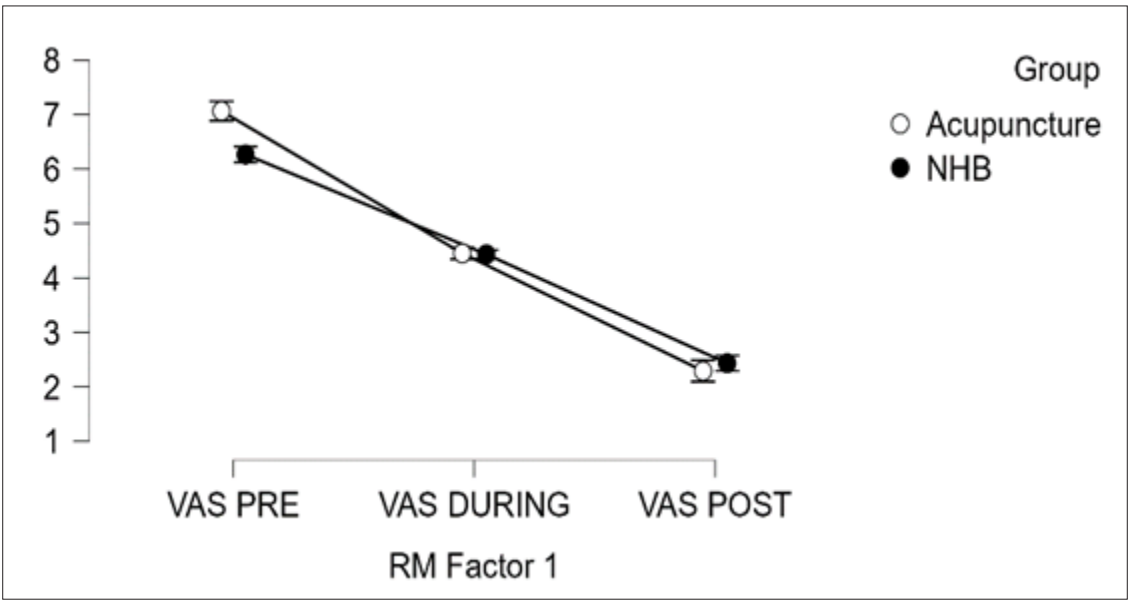


Figure 1. Profile Plots showing Changes in Groups Pre, Mid and Post-intervention of VAS

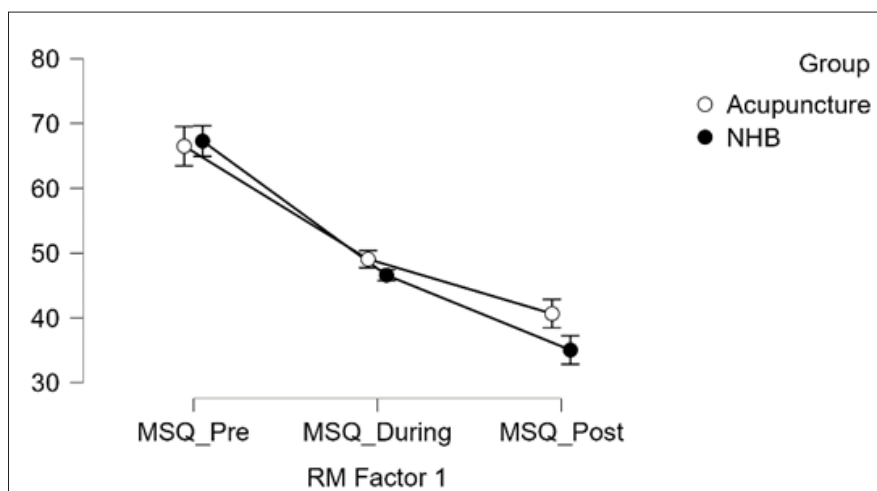


Figure 2. Profile Plots showing Changes in Groups Pre, Mid and Post-intervention of MSQ

Discussion

The present study investigated the comparative effects of NHB and acupuncture following 60 days of intervention in the management of PD. The findings suggested that both interventions are equally effective. Results suggested a significant reduction in the mean score in all three comparisons: pre vs mid, mid vs post, and pre vs post in both groups.

Pain is a personalised complex experience, particularly difficult to investigate, manipulate, and manage. A possible mechanism in dysmenorrhea occurring during acupuncture is related to the study findings proposed by Pomeranz, which state that during acupuncture, C and A- δ afferent fibres in the muscles are activated.²⁷ These afferent fibres transmit the signals to the spinal cord and are then further carried to the midbrain through the afferent pathways. The perception of pain emerges from the resulting flow and combination of this data amongst particular brain areas, leads to a trade in the appreciation of pain. Descending pain-modulatory system is the key anatomical network for the underlying capacity of pain.²⁸ This descending pain-modulatory system is concerned with brain stem structures which alter women's experience of pain ensuing from dysmenorrhea. Prostaglandin F₂ α (PGF₂ α), responsible for dysmenorrhea and associated symptoms such as diarrhoea, headache, backache, nausea, and vomiting can be defined by means of entry of prostaglandin metabolites and PG into the systemic circulation. The associated enhancement in dysmenorrhea-related signs and symptoms is influenced by a further mechanism arising from a launch of neurotransmitters in relation to the integration of data from the neural pathways as a reaction to needle stimulation. When these signals reach the hypothalamus and pituitary, they activate a neuroendocrine response. A study done on an animal model showed that stimulation of acupuncture factors SP8, SP6, and CV4 was proven to modify neuro-endocrine

activity along with luteinizing hormone, follicle-stimulating hormone, progesterone and estradiol.²⁹

Above mentioned evidence clearly explains the effect of acupuncture in PD on the reduction of pain and systemic symptoms.

Patients with symptoms of pain have lowered parasympathetic activity.³⁰ Application of neutral spinal bath and neutral spinal spray (NSS) improves sympathovagal balance³¹ by enhancing parasympathetic activity.³² Application of neutral temperature causes peripheral vasodilation by increasing cutaneous circulation induced by parasympathetic activity.³³ Whirlpool baths and warm leg immersions are advantageous in reducing pain.³⁴ It has been seen that the application of lukewarm water-soaked gauze on the suprapubic region results in significant effects on postoperative urinary retention and also significantly reduces the need for urinary catheterisation.³⁵ The neutral compress sometimes proves more serviceable in relieving the pain of neuralgia than hot and cold applications. Hence it can be concluded that the application of neutral water will increase the parasympathetic activity and maintain vascular tone and functional activity of pelvic organs, thereby decreasing the pain.

Limitation of the Study

The present study was done only on patients with a regular menstrual cycle of 30 days and 3-5 days of bleeding phase. Hence the results cannot be generalised.

Scope for Further Research

Further research can be done on objective variables and hormonal assessment in association with dysmenorrhea.

Conclusion

The present study concluded that NHB was equally effective as acupuncture, given for 60 days, by effectively reducing the severity of dysmenorrhoeic pain and associated

symptoms among young females suffering from PD. Thus, acupuncture and NHB can be safely used as alternative and complementary therapy in the management of PD.

Acknowledgement

I would take this opportunity to thank my dear parents and brother for their love and constant support. My special gratitude is extended to Alva's College of Naturopathy and Yogic Sciences, Moodbidri, India for giving me an opportunity to carry out the research; and to my teachers, friends, and juniors for their motivation and support.

Source of Funding: Self-funded

Conflict of Interest: None

References

- Dutta D, Konar H. DC Dutta's textbook of gynecology. 7th ed. Jaypee Brothers Medical Publishers (P) Ltd; 2016. [Google Scholar]
- Ju H, Jones M, Mishra G. The prevalence and risk factors of dysmenorrhea. *Epidemiol Rev.* 2014;36(1):104-13. [PubMed] [Google Scholar]
- Berkley KJ. Primary dysmenorrhea: an urgent mandate. *Pain.* 2013;21(3). [Google Scholar]
- Padubidri VG, Daftray S. Shaw's textbook of gynaecology. 16th ed. Elsevier; 2015.
- Agarwal AK, Agarwal A. A study of dysmenorrhea during menstruation in adolescent girls. *Indian J Community Med.* 2010;35(1):159. [PubMed] [Google Scholar]
- Pan S, Wang S, Li J, Yuan H, Xue X, Liu Y, Yue Z. Moxibustion for primary dysmenorrhea: an adjuvant therapy for pain relief. *Evid Based Complement Alternat Med.* 2022;2022:6864195. [PubMed] [Google Scholar]
- Abubakar U, Zulkarnain AI, Samri F, Hisham SR, Alias A, Ishak M, Sugiman H, Ghazali T. Use of complementary and alternative therapies for the treatment of dysmenorrhea among undergraduate pharmacy students in Malaysia: a cross sectional study. *BMC Complement Med Ther.* 2020;20(1):285. [PubMed] [Google Scholar]
- Gharloghi S, Torkzahrani S, Akbarzadeh AR, Heshmat R. The effects of acupressure on severity of primary dysmenorrhea. *Patient Prefer Adherence.* 2012;6:137-42. [PubMed] [Google Scholar]
- Rastogi R. Naturopathy in India: current status and future challenges. *Ann Ayurved Med.* 2012;1(4). [Google Scholar]
- Sengar M, Bhutani M, Aggarwal D, Kochupillai V. Cancer treatment: role of yoga, naturopathy and prayer. *Health Admin.* 2012;17(1):151-7. [Google Scholar]
- Hough HJ, Dower C, O'Neil EH. Profile of a profession: naturopathic practice. Center for the Health Professions, University of California, San Francisco; 2001. [Google Scholar]
- Agrawal AL, Sharma GN. Clinical practice of acupuncture. 2nd ed. CBS Publishers & Distributors Pvt Ltd; 2019.
- Rahmania S, Shetty V, Ragavendrasamy B. Neutral douche: a hydrotherapeutic tool to manage pain and systemic symptoms in primary dysmenorrhea - a randomised controlled study. *J Complement Integr Med.* 2021;18(1):209-16. [PubMed] [Google Scholar]
- Iorno V, Burani R, Bianchini B, Minelli E, Martinelli F, Ciatto S. Acupuncture treatment of dysmenorrhea resistant to conventional medical treatment. *Evid Based Complement Altern Med.* 2008;5(2):227-30. [PubMed] [Google Scholar]
- Jayasuriya A. Clinical acupuncture A to Z. B Jain Publishers (P) Ltd; 2002. [Google Scholar]
- Helms JM. Acupuncture for the management of primary dysmenorrhea. *Obstet Gynecol.* 1987;69(1):51-6. [PubMed] [Google Scholar]
- Bahadorfar M. A study of hydrotherapy and its health benefits. *Int J Res.* 2014;1(8). [Google Scholar]
- Shrestha RL, Sujatha KJ. Effect of cold hip bath on autonomic variables in healthy individuals - a randomized control trial. *J Res Educ Indian Med.* 2017. [Google Scholar]
- Bakhru HK. Naturopathy for longevity. 13th ed. Mumbai: Jaico Publishing House; 2018.
- Bhagat PT. Alternative therapies. 1st ed. Jaypee brothers Medical Publishers (P) Ltd; 2004.
- Welton W. Treatment of dysmenorrhoea. *Prov Med J Retrospect Med Sci.* 1843;6(133):50-1. [PubMed] [Google Scholar]
- Osayande AS, Mehulic S. Diagnosis and initial management of dysmenorrhea. *Am Fam Physician.* 2014;89(5):341-6. [PubMed] [Google Scholar]
- Larroy C. Comparing visual-analog and numeric scales for assessing menstrual pain. *Behav Med.* 2002 Winter;27(4):179-81. [PubMed] [Google Scholar]
- Chesney MA, Tasto DL. The development of the menstrual symptom questionnaire. *Behav Res Ther.* 1975 Oct;13(4):237-44. [PubMed] [Google Scholar]
- Agrawal AL, Sharma GN. Advanced acupuncture therapy. 1st ed. CBS Publishers & Distributors Pvt Ltd; 2009.
- Jindal SR. Nature cure treatments. 7th ed. Institute of Naturopathy & Yogic Sciences; 1994.
- Pomeranz B, Chiu D. Naloxone blockade of acupuncture analgesia: endorphin implicated. *Life Sci.* 1976;19(11):1757-62. [PubMed] [Google Scholar]
- Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron.* 2007;55(3):377-91. [PubMed] [Google Scholar]
- Liu F, Xiong J, Huang G, Wang W. [Study on the underlying mechanism of acupuncture in regulating neuroendocrine activity in dysmenorrhea rats]. *Zhen*

- Ci Yan Jiu. 2009;34(1):3-8. Chinese. [PubMed] [Google Scholar]
30. Koenig J, Jarczok MN, Ellis RJ, Warth M, Hillecke TK, Thayer JF. Lowered parasympathetic activity in apparently healthy subjects with self-reported symptoms of pain: preliminary results from a pilot study. *Pain Pract.* 2015;15(4):314-8. [PubMed] [Google Scholar]
31. Goley A, Mooventhan A, Manjunath NK. Comparative study on effect of neutral spinal bath and neutral spinal spray on blood pressure, heart rate and heart rate variability in healthy volunteers. *J Complement Integr Med.* 2018;16(2). [PubMed] [Google Scholar]
32. Avanthika G, Sujatha KJ, Shetty P. Immediate effect of cold and neutral spinal spray on autonomic functions in healthy volunteers – a comparative study. *J Dent Med Sci.* 2017;16(11).
33. Soni K, Shetty P, Sujatha KJ. A comparative study on effects of neutral and cold underwater massage on the physiological parameters of healthy individuals. *J Dent Med Sci.* 2016;15(9).
34. Munguía-Izquierdo D, Legaz-Arrese A. Exercise in warm water decreases pain and improves cognitive function in middle-aged women with fibromyalgia. *Clin Exp Rheumatol.* 2007;25(6):823-30. [PubMed] [Google Scholar]
35. Afazel MR, Jalali E, Sadat Z, Mahmoodi H. Comparing the effects of hot pack and lukewarm-water-soaked gauze on postoperative urinary retention; a randomized controlled clinical trial. *Nurs Midwifery Stud.* 2014;3(4). [PubMed] [Google Scholar]