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Osteopathic Manipulative Treatment of Primary Dysmenorrhea and Related Factors: A Randomized Controlled Trial

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ABSTRACT

Objectives: *This study is aimed to evaluate if the osteopathic manipulative treatment (OMT) is effective in patients with primary dysmenorrhea (PD).* ***Methods:*** *Randomized single-blinded controlled trial with OMT group and light-touch treatment (LTT) group. Recruited women were 18-40 years (mean age 27 years), with regular menstrual cycle, normal body mass index (BMI), and a medical diagnosis of PD.* ***Intervention:*** *Patients received five OMT or five LTT over a menstrual cycle. The primary outcomes were average menstrual pain assessed by the numeric rating scale (NRS), the duration of pain, and quality of life (QoL) assessed by the SF-12 Short Form Health Survey and Patient Global Impression Change (PGIC). The secondary outcomes were NSAIDs intake, hours of absence from school/work, and menstrual-related symptoms.* ***Results:*** *31 subjects were enrolled, of which five were excluded and the remaining 26 were randomized. Patients in OMT group had significant improvement in every outcome, including the average menstrual pain that decreased from 5.35 ± 0.28 to 1.98 ± 0.24 (-63.0%; $p<0.001$). The mean SF-12 physical component score (PCS) improved from 31.35 ± 1.70 to 49.56 ± 1.92 (+58.1%, $p<0.001$), the mean SF-12 mental component score (MCS) improved from 38.36 ± 1.16 to 52.04 ± 0.94 (+35.7%; $p<0.001$). LTT group showed no improvements.* ***Conclusion:*** *OMT was effective in reducing menstrual pain and improving Quality of Life of dysmenorrheic women.*

Keywords: Osteopathic manipulative treatment, Primary dysmenorrhea, Menstrual pain, Chronic pelvic pain, Quality of life, Randomized controlled trial

INTRODUCTION

Primary dysmenorrhea (PD) is a menstrual cramping pain not associated to pelvic pathologies [1]. It is a common gynaecological complaint that may occur in a wide range (16.8% to 81.0%) of menstruating women, and it is often characterized by associated symptoms, like nausea, vomit, diarrhoea, legs, or abdomen swelling, breasts tension and headache [1].

Risk factors include smoking, earlier age at menarche, long menstrual cycle length, BMI>30, alcohol consumption, and nulliparity [2].

PD has a huge socioeconomic impact, with up to 30% of working/studying women that lose 1-2 days per month in the USA, resulting in 600 million working hours of absenteeism and up to $2 billion losses per year [3]. Even if PD has a negative impact on female population, it seems to be accepted like a constituent part of woman-being, and the gynaecologic health care provider is barely consulted for possible solutions [4].

The physiopathology of PD is still discussed and not completely certain [5]. However, increased level of prostaglandins in menstrual blood flow is demonstrated to play an important role [1] and women with PD have prostaglandin levels twice times higher compared to non-dysmenorrheic women [6]. The release of arachidonic acid during menstruation triggers overproduction of uterine prostaglandins and leukotrienes, with myometrial smooth muscle contraction and ischemia of uterine arterioles [7]. Chemokines, cytokines, growth factors, oxytocin and vasopressin acting both locally and systemically influence uterine physiology [7]. Recent evidences demonstrated significant difference between women suffering from PD and non-dysmenorrheic women in central nerve activity induced by noxious skin stimulation, brain metabolism and morphology of grey matter [8]. These findings suggested a correlation between PD and central sensitivity to pain [9].

Nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal contraceptives represent the gold standard in alleviating menstrual pain and relaxing uterine muscles [10]. Unfortunately, they show a failure rate of 20-25% and a wide range of side effects [7], thus other approaches have been explored [7].

Limited evidences support manipulative and physical therapy for PD [11]. Spinal manipulation relieves pain [12] and apparently reduces the circulating plasma levels of prostaglandins [13], but the results are not conclusive enough to recommend spinal manipulation for PD [4].

A considerable number of evidences shows the effectiveness of OMT on chronic pain, and the association between spinal manipulation and reduced circulating plasma levels of prostaglandins [12], cytokines and other inflammatory signals [13]. Moreover, the high-velocity low-amplitude (HVLA) techniques applied to lumbosacral and cervical spine are demonstrated to be related to significant reduction of corticospinal and spinal reflex excitability, thus suggesting transient cortical plastic changes [14]. Thus, OMT might represent an effective addition to the available tools for treating patients with PD. Only limited experimental evidence supporting this contention is so far available [15].

This study was aimed to investigate the efficacy of Osteopathic Manipulative Treatment (OMT) compared to Light-Touch Treatment (LTT) in influencing menstrual pain level, QoL and menstrual-related factors in patients with PD.

MATERIALS AND METHODS

This randomized single-blinded controlled trial was conducted at the Centro di Medicina Osteopatica (CMO), Istituto Superiore di Osteopatia (ISO) in Milan, Italy. Before the beginning of the study, all the study procedures were approved by a board of ISO experts, according to the Declaration of Helsinki's standards and the guidelines for Good Clinical Practice.

The participants were Italian women, recruited between 2015 and 2016 through word of mouth, flyers, and video advertising.

The inclusion criteria were age between 18-40 years, regular menstrual cycle (28 ± 7 days), BMI between 20-30, and medical diagnosis of PD. The exclusion criteria were pregnancy, medical diagnosis of secondary dysmenorrhea [3], self-declared alcohol or drug misuse problems and recruitments in other clinical studies.

Subjects were randomly assigned to two groups by using a sealed envelope: the study group (n=13) received OMT, and the control group (n=13) received LTT. The randomization sequence was generated by an external operator by using an online software (random.org).

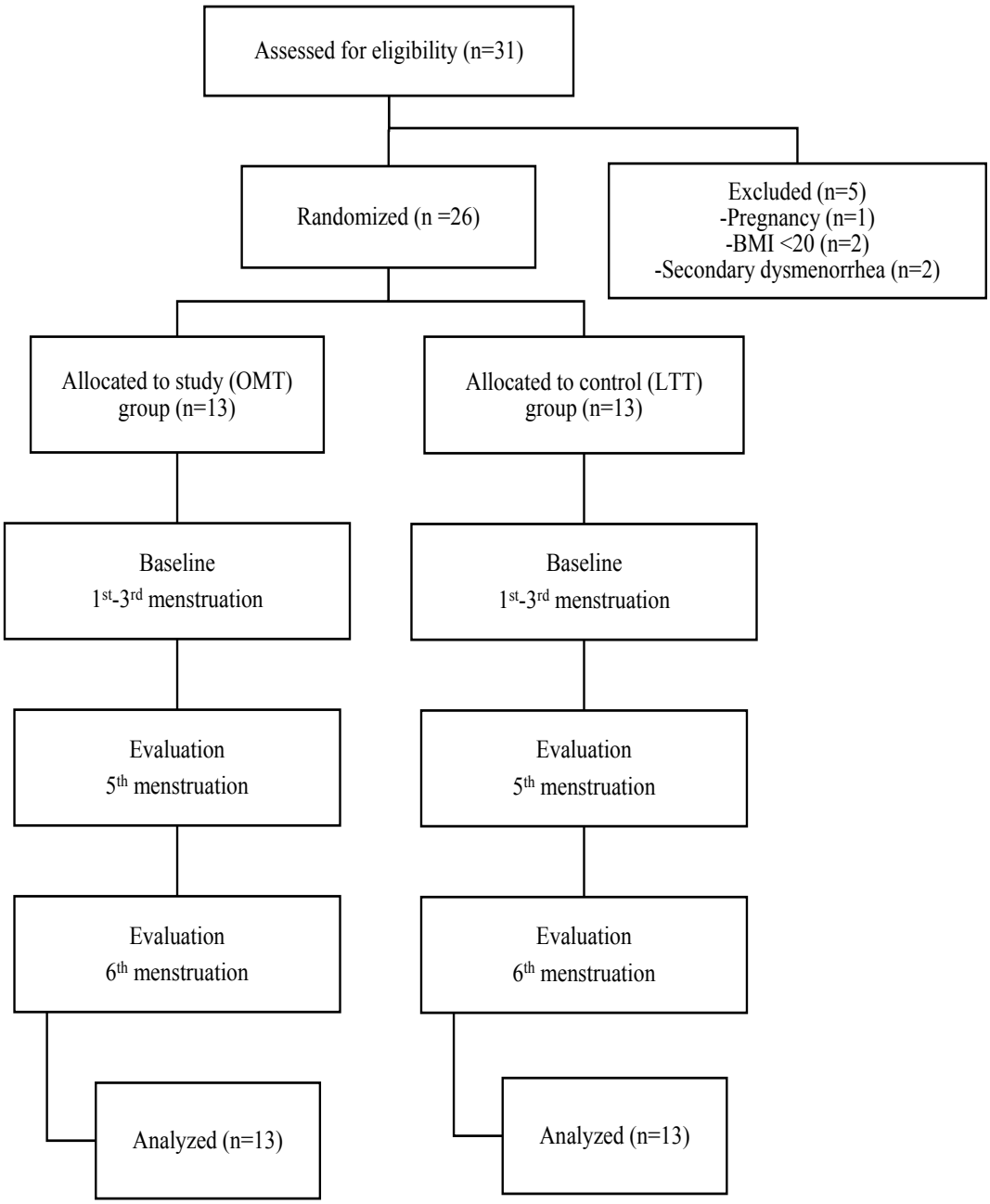

Figure 1 Flow chart of subjects in the study

During the baseline period (1st-3rd menstrual cycle), no treatments were given; however, the patients were required to fulfil the Numeric Rating Scale (NRS) for all the first five days of every menstrual cycles. Starting from the 4th menstrual cycle, the patients were treated 5 times (every 5 ± 1 days) and evaluated during the first five days of their 5th menstruation. After a month without any treatment, patients were subsequently evaluated at their 6th menstruation. The data were collected by external operator blinded to allocation treatment.

The mean value of collected data was calculated during the first three menstruations (baseline) and then compared to the data of the 5th and 6th menstruations (Figure 2).

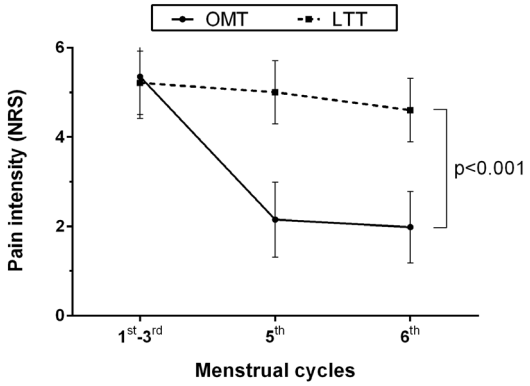

Figure 2 Menstrual pain levels between the baseline and 6th menstruation

According to osteopathic literature, the OMT protocol includes myofascial release, craniosacral manipulation, HVLA techniques [12], balanced ligamentous tension, muscle energy, strain-counterstrain and soft tissue techniques. OMT group was treated according to the clinical findings following the osteopathic evaluation rather than to a pre-determined protocol [7].

The LTT properly imitated the osteopathic treatment with a light-touch contact (Figure 3).

All participants signed a written informed consent, after being informed about the procedures of study. Study's procedures kept all the patients blinded to the allocation treatment for the whole trial.

Primary outcomes were the menstrual pain intensity, assessed by the NRS, that is an 11-point scale (from 0=no pain to 10=the worst pain ever felt), and QoL assessed by the SF-12. The average NRS score was assessed on the first five days of menstrual cycle and on the proportion of "days out of five" in which the subjects rated respectively NRS ≥ 5 and NRS>0.

According to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations, we considered reduction in pain as moderate ($\geq 30\%$) or substantial ($\geq 50\%$) [16]. We assessed the PGIC as a primary outcome, measured by a 7-point scale (from 1=very much improved to 7=very much worse) [17].

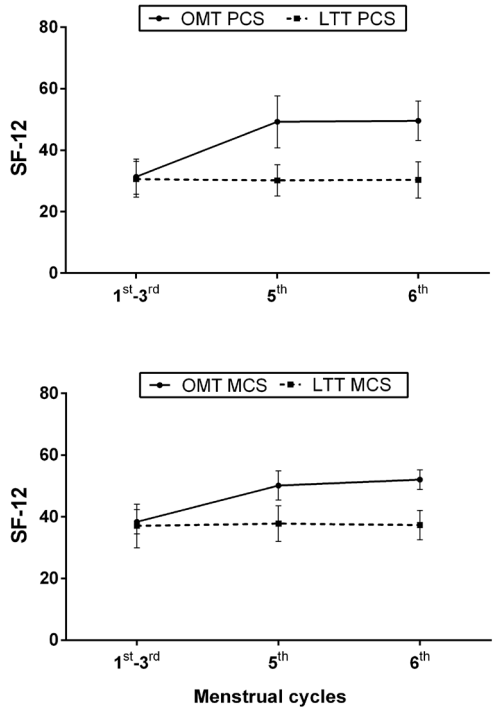

Figure 3 Patient' QoL evaluated by the SF-12 between the baseline and the 6th menstrual cycle

Secondary outcomes included the effect of treatment on menstrual-related symptoms, such as nausea/vomiting, diarrhoea, breast tension, headache, fatigue, NSAIDs intake and hours of absence from school/work were recorded on a monthly diary.

An external assessor conducted statistical analyses in a blinded fashion by using R software (R core Team, 2017). Baseline differences among groups were detected using the Fisher's exact test for categorical variables and the Welch's t-test otherwise. A Generalized Estimating Equations (GEE) analysis and Wald Chi-Square test were used to evaluate the main effects of the treatment groups (TR), time (TI) and their interaction (TR × TI) on the outcome measures included as dependent variables. TR and TI levels were included in the model according to the so-called "dummy coding approach", with the OMT group and T0 coded as 0 respectively. Smoking (dichotomous), BMI (continuous) and the length of menstrual cycle (continuous) were included as independent covariates in the analysis of pain level and QoL. No covariates were included in the analysis of secondary outcomes. The statistical significance level (α) was set at 0.01.

RESULTS

A total of thirty-one subjects were evaluated, five were excluded and twenty-six women were enrolled and randomized to OMT (n=13) or LTT group (n=13). All of them completed the study, no drop out were registered and no adverse events occurred (Figure 1). All patients were nulliparous and Caucasians.

Descriptive statistics for anthropometric data at the baseline are reported in Table 1. There were no significant differences between the two groups. Further, GEE analysis showed no differences at baseline neither for the primary (Table 2), nor for the secondary outcomes (Table 3).

At the 5th as well as at the 6th menstruation GEE analysis indicated a significant interaction TR × TI ($p<0.001$) for the average NRS score, the proportion of days in which the subjects rated NRS ≥ 5 and the SF12-PCS and MCS score. At the 6th menstruation no significant interaction was observed for the proportion of days in which the subjects rated NRS>0. The results could be interpreted as a significant pain reduction and an improvement of QoL over the time for the OMT group as compared with controls (Tables 2-4). According to the IMMPACT recommendations, at the 6th menstruation OMT group reported "moderate" or "substantial" reduction of the mean menstrual pain, 2/13 (15%) and 11/13 (85%) respectively.

Table 1 Anthropometric data of dysmenorrheic women at baseline

Variables	OMT group (n=13)		LTT group (n=13)		p-value
	mean	SE	mean	SE	
Age (y)	25.92	5.63	27.84	6.93	0.445 [a]
BMI (Kg/m^2)	22.37	2.17	21.89	1.43	0.516 [a]
Age at menarche (y)	11.07	1.03	11.69	0.94	0.127 [a]
Length of the menstrual cycle (d)	28.84	1.34	27.84	1.21	0.058 [a]
Tobacco use (%)	46.15	-	7.69	-	0.073 [b]
Dyspareunia (%)	61.54	-	46.15	-	0.695 [b]

Y: Years; BMI: Body Mass Index; D: Days; NRS: Numeric Rating Scale; OMT: Osteopathic Manipulative Treatment; LTT: Light-Touch Treatment; SE: Standard Error; A: Welch's P-value analysis; B: Fisher P-value analysis.

Table 2 Effect of osteopathic manipulative treatment on primary outcomes between baseline and the 6th menstruation

Primary outcomes	Group	Baseline (M ± SE)	6th (M ± SE)	Group [a]	Time [b]	Group × Time [c]
Pain Intensity (NRS)	OMT	5.35 ± 0.28	1.98 ± 0.24	p=0.730	p<0.001	p<0.001
	LTT	5.21 ± 0.21	4.60 ± 0.21	W=0.119	W=118.806	W=70.171
Duration of Dysmenorrheal pain (>0) [d]	OMT	0.93 ± 0.02	0.60 ± 0.04	p = 0.185	p<0.001	p=0.817
	LTT	0.98 ± 0.01	0.83 ± 0.02	W=1.761	W=27.560	W=0.053
Duration of Dysmenorrheal pain (³5) [d]	OMT	0.59 ± 0.04	0.11 ± 0.04	p=0.750	p<0.001	p<0.001
	LTT	0.61 ± 0.04	0.53 ± 0.04	W=0.102	W=19.128	W=13.945
SF-12 (PCS)	OMT	31.35 ± 1.70	49.56 ± 1.92	p=0.768	p<0.001	p<0.001
	LTT	30.54 ± 1.73	30.34 ± 1.74	W=0.087	W=50.397	W=41.186
SF-12 (MCS)	OMT	38.36 ± 1.16	52.04 ± 0.94	p=0.596	p<0.001	p<0.001
	LTT	37.02 ± 2.10	37.28 ± 1.42	W=0.281	W=261.218	W=63.105

Results of Generalized Estimated Equation (GEE) analysis adjusted for covariates. Estimated marginal mean (M) ± standard error (SE) at baseline and 6th menstruation. Bold letters indicate significant group × time interaction. OMT: osteopathic manipulative treatment; LTT: light touch treatment; SF-12 PCS: physical component score; SF12 MCS: mental component score. ap-value of group effect at baseline; W: Wald chi square test. [d] proportion of days out of five in which the subjects rated respectively NRS>0 and NRS ≥ 5. [C] p-value of group x time; W: Wald chi square test. [b] p-value of time effect; W: Wald chi square test.

As suggested by the IMMPACT recommendations, at the 6th menstruation all the patients completed the PGIC by reporting the self-perceived improvement: OMT group showed a mean PGIC value of 2.2 ± 1.1 (“very improved”), while LTT group showed a mean PGIC value of 4.2 ± 0.7 (“no changes”).

Table 3 Effect of osteopathic manipulative treatment on secondary outcomes over the time

Secondary outcomes	Group	M ± SE			Group [a]	Time [b]		Group × Time [c]	
		Baseline	5th	6th		5th	6th	5th	6th
NSAIDs	OMT	0.92 ± 0.07	0.53 ± 0.13	0.30 ± 0.12	p=1.00	p=0.022	p=0.003	p=0.022	p=0.003
	LTT	0.92 ± 0.07	0.92 ± 0.07	0.92 ± 0.07	W=0.000	W=5.265	W=9.024	W=5.265	W=9.024
Absence from school/work	OMT	0.92 ± 0.07	0.23 ± 0.11	0.07 ± 0.07	p=0.547	p=0.001	p<0.001	p = 0.001	p<0.001
	LTT	0.84 ± 0.10	0.84 ± 0.10	0.84 ± 0.10	W=0.364	W=10.468	W=12.436	W=10.468	W=12.436
Nausea/Vomit	OMT	0.76 ± 0.11	0.15 ± 0.10	0.00 ± 0.00	p=1.00	p=0.001	p < 0.001	p=0.001	p<0.001
	LTT	0.76 ± 0.11	0.76 ± 0.11	0.69 ± 0.13	W=0.000	W=10.739	W=2579.162	W=10.739	W=1983.567
Diarrhea	OMT	0.69 ± 0.12	0.23 ± 0.11	0.15 ± 0.10	p=0.681	p=0.005	p=0.002	p=0.028	p=0.013
	LTT	0.61 ± 0.13	0.53 ± 0.13	0.53 ± 0.13	W=0.169	W=8.030	W=9.180	W=4.824	W=6.186
Breasts tension	OMT	0.76 ± 0.11	0.38 ± 0.13	0.23 ± 0.11	p=0.399	p=0.011	p=0.002	p=0.011	p=0.002
	LTT	0.61 ± 0.13	0.61 ± 0.13	0.61 ± 0.13	W=0.710	W=6.467	W=9.557	W=6.467	W=9.557
Headache	OMT	0.76 ± 0.11	0.23 ± 0.11	0.07 ± 0.07	p=0.115	p=0.002	p=0.001	p=0.001	p=0.004
	LTT	0.46 ± 0.13	0.53 ± 0.13	0.38 ± 0.13	W=2.483	W=9.557	W=10.468	W=10.614	W=8.168
Fatigue	OMT	0.83 ± 0.05	0.47 ± 0.11	0.47 ± 0.11	p=0.778	p=0.005	p=0.005	p=0.005	p=0.005
	LTT	0.85 ± 0.10	0.52 ± 0.14	0.52 ± 0.14	W=0.080	W=7.755	W=7.755	W=7.755	W=7.755

Results of generalized estimated equation analysis (GEE). Mean (M) ± Standard Error (SE) at baseline, 5th and 6th menstruation. OMT: Osteopathic Manipulative Treatment; LTT: Light Touch Treatment; [a] p-value of group effect at baseline; W: Wald Chi square test. [b] p-value of time effect; W: Wald Chi square test. [C] p-value of group × time; W: Wald Chi square test.

At the 6th menstruation GEE analysis exhibits a significant interaction TR × TI (p<0.001) for all the secondary outcome in OMT group compared with LTT group, except for the presence of diarrhoea (Table 3).

Table 4 Effect of osteopathic manipulative treatment on primary outcomes over the time

Primary outcomes	Group	M ± SE			Group [a]	Time [b]		Group × Time [c]	
		Baseline	5th	6th		5th	6th	5th	6th
Pain Intensity (NRS)	OMT	5.35 ± 0.28	2.15 ± 0.25	1.98 ± 0.24	p=0.730	p<0.001	p<0.001	p<0.001	p<0.001
	LTT	5.21 ± 0.21	5.00 ± 0.21	4.60 ± 0.21	W=0.119	W=140.468	W=118.806	W=114.422	W=70.171
Duration of Dysmenorrheal pain (>0) [d]	OMT	0.93 ± 0.02	0.64 ± 0.04	0.60 ± 0.04	p=0.185	p<0.001	p<0.001	p<0.001	p=0.817
	LTT	0.98 ± 0.01	0.98 ± 0.01	0.83 ± 0.02	W=1.761	W=32.668	W=27.560	W=32.668	W=0.053
Duration of Dysmenorrheal pain (³5) [d]	OMT	0.59 ± 0.04	0.14 ± 0.05	0.11 ± 0.04	p=0.750	p<0.001	p<0.001	p<0.001	p<0.001
	LTT	0.61 ± 0.04	0.54 ± 0.05	0.53 ± 0.04	W=0.102	W=22.864	W=19.128	W=16.762	W=13.945
SF-12 (PCS)	OMT	31.35 ± 1.70	49.21 ± 2.05	49.56 ± 1.92	p=0.768	p<0.001	p<0.001	p<0.001	p<0.001
	LTT	30.54 ± 1.73	30.17 ± 1.50	30.34 ± 1.74	W=0.087	W=49.733	W=50.397	W=45.038	W=41.186
SF-12 (MCS)	OMT	38.36 ± 1.16	50.12 ± 1.41	52.04 ± 0.94	p=0.596	p<0.001	p<0.001	p<0.001	p<0.001
	LTT	37.02 ± 2.10	37.79 ± 1.72	37.28 ± 1.42	W=0.281	W=50.597	W=261.218	W=25.778	W=63.105

Results of generalized estimated equation analysis (GEE) adjusted for covariates. Estimated marginal mean (M) ± Standard Error (SE) at baseline, 5th and 6th menstruation. OMT: Osteopathic Manipulative Treatment; LTT: Light Touch Treatment; SF-12 PCS: Physical Component Score; SF12 MCS: Mental Component Score. [a] p-value of group effect at baseline; W: Wald chi square test. [b] p-value of time effect; W: Wald chi square test. [c] p-value of group × time; W: Wald chi square test. [d] proportion of days out of five in which the subjects rated respectively NRS>0 and NRS ≥ 5.

DISCUSSION

This study was conducted to investigate the OMT efficacy in relieving pain and improving the QoL of women suffering from PD.

OMT group patients, differently from the LTT group patients, significantly improved in both the primary outcomes: decreased menstrual pain intensity and improved QoL, as confirmed by increased PGIC scores. Moreover, subjects treated by OMT showed statistically significant decrease in the average NSAIDs intake, hours of absence from school/work, and menstrual-related symptoms (Tables 3 and 4). It is likely to say that OMT could reduce the huge socio-economic impact due to PD [3].

These results are in agreement with those reported by Schwerla, et al. [15]. Moreover, we improved the internal validity of Schwerla's study, minimizing the possible confounding effect of a waiting list group by assessing a placebo-controlled trial [18]. Indeed, there is evidence suggesting that pain is the major outcome on which a statistically significant placebo effect was observed, when assuming that a waiting list cannot differentiate the specific OMT effects and LTT placebo effects [19].

Experimental evidence has shown that the dynamic impulse of a spinal manipulation has an impact on proprioceptive primary afferent neurons of para-spinal tissues and can affect pain processing by altering the facilitated central state of the spinal cord [20]. Moreover, according to previous studies on the effects of spinal manipulation on PD patients [12], we assume that osteopathic manipulation of the D10-L2 and S2-S4 spinal segments carried out in this study, could produce an autonomic response, resulting in decreased uterine contractions, increased blood flow into the pelvic region, and reflex inhibition of pain [21].

Sensitisation of the spinal segments associated to the uterus may have caused greater enhancement of afferent inputs, resulting in visceral hyperalgesia [22]. The manipulation of the muscular, visceral and joint structures, sharing the same sensory and motor pathways, could have involved serotonin and norepinephrine receptors in the spinal cord [23], and then reduced the nociceptive convergence between the D10-L2 and S2-S4 spinal segments [14,24].

Since the long-lasting inflammation of the lumbopelvic joints, ligaments and muscles affected by PD [2] supports both the peripheral and central sensitization [20], it is possible to assume that manipulation of these tissues could be linked to some functional changes of the central nervous system [25]. This hypothesis is supported by some *in*

vivo studies concerning the effects of manipulation on inflammation-induced hyperalgesia, via descending inhibitory mechanisms [23].

To evaluate the role of central sensitization, as suggested by Akinci, future studies should assess other outcomes, such as the central sensitization inventory (CSI), the quantitative sensory testing (QST), and questionnaires on psychosocial correlates [25].

A possible underlying mechanism for the effectiveness of OMT on menstrual pain levels, is consistent with an increasing body of studies explores the response of serotonin [26] and other biomarkers to OMT for several musculoskeletal conditions [12], including plasma prostaglandin levels in women with PD [13]. Since PD is associated to inflammation, the pain reduction might reflect anti-inflammatory mechanisms triggered by OMT. The reduction of menstrual pain and other menstrual-related symptoms impacts on the patient's QoL. In fact, the monthly pain experienced by women with PD considerably affected multiple aspects of their personal life [3].

Otherwise the psychological distress caused by pain could exacerbate the pain itself [27]. If arousing positive emotions reduce pain perception [28], it could be said that arousing negative emotions/affective increase pain facilitation [29] due to thalamic sensitization associated with chronic visceral pain [30].

CONCLUSION AND FUTURE STUDIES

To our knowledge, this is the first study evaluating the OMT effects on PD women compared to LTT effects. Moreover, considering PD as a chronic pain [16], the primary outcomes were based on the IMMPACT recommendations, that have been specifically developed to facilitate the clinical data interpretation about the efficacy and effectiveness of chronic pain treatment [16].

The most significant limitation of this trial is related to the small sample size and to the fact that the women enrolled are not representative of the entire population affected by PD, since they were nulliparous and young adult.

Future studies should include the assessment of OMT long-term effect on menstrual pain and quality of life.

In conclusion, our findings provided evidence that OMT is effective in relieving menstrual pain in women with PD, enhancing their QoL, and reducing the number of painful days, as well as the average NSAIDs intake, the hours of absence from school/work, and menstrual-related symptoms. Therefore, OMT may represent a therapeutic strategy for PD management.

DECLARATIONS

Author contributions

Dario Zecchillo and Viviana Pisa gave substantial contribution to the conception and design of the work. Dario Zecchillo was involved in the data acquisition. Viviana Pisa and Stefano Uberti were involved in data analysis. Andrea Acquati, Alessandro Aquino and Stefano Uberti were involved in data interpretation. Dario Zecchillo, Silvia Ratti and Stefano Uberti drafted the work. Andrea Acquati, Alessandro Aquino and Viviana Pisa gave critical revision of the work. All authors gave final approval of the version to be published. All authors agreed to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

All authors declare no conflict of interest.

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