Transvaginal Low Intensity Shockwave Therapy in Endometriosis (T-LISTE) : protocol for a pilot trial

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ABSTRACT

Background

Endometriosis is a frequent disorder in women of childbearing age. Standard medical and surgical treatments are often unsatisfactory. Shockwave therapy has been suggested as a possible novel treatment. There is no clinical data however to support this approach. This article describes the research protocol for a pilot interventional trial aiming to evaluate transvaginal low intensity shockwave therapy in women with endometriosis.

Methods

Adult women (anticipated N = 60) suffering from endometriosis will be randomly allocated in a 1:1 ratio to an intervention group and a control group. The intervention group will receive 4 sessions of transvaginal low intensity radial shockwave therapy. The control group will receive 4 sham procedures. Assessment will be carried at 1, 3 and 6 months. The primary endpoint is the visual analog score for pelvic pain.

Conclusion

This monocentric single blinded randomized controlled pilot trial will be the first to assess transvaginal low intensity shockwave therapy as a novel treatment for endometriosis.

KEYWORDS : Endometriosis ; Adenomyosis ; Pelvic pain ; Dysmenorrhea ; Dyspareunia ; Shockwave Therapy.

ABBREVIATIONS : SWT (shockwave therapy) ; DIE (deep infiltrating endometriosis) ;HIFU (high intensity focalized ultrasound) ; ART (assisted reproductive technology) ; VAS (visual analog scale) ;IUD (intrauterine device).

INTRODUCTION

Endometriosis is defined as the ectopic localisation of endometrium. Prevalence is estimated at 10 % to 15 % of women of reproductive age and 70 % of women with chronic pelvic pain[1]. Symptoms include dysmenorrhea, dyspareunia, bladder and rectal pain that can severely alter quality of life. 11% to 19% of women with endometriosis derive no pain relief at all from medical therapy[2]. Surgery, especially excision of deep infiltrating endometriosis (DIE) can be challenging, and complications rates can be high. Major complications after colorectal segmental resection of bowel endometriosis occurs in 11 % of patients[3]. Moreover, long-term urinary and digestive side effects are common following surgery[4][5]. There is a need for new, effective and safe therapeutic methods. High intensity focalized ultrasound (HIFU) and radiofrequency ablation are being evaluated[6][7][8][9][10][11]. Shockwave therapy (SWT) has been suggested as a novel approach to treat endometriosis.

RATIONALE

The theoretical basis for the use of SWT in endometriosis has been developed recently[12]. Basically high intensity focalized shockwaves could be directed to the lesions to obtain a disruptive effect, or low intensity radial or focused shockwaves could be applied to achieve pain relief via neuromodulatory, antioxydant and antiinflammatory effects. This trial aims to evaluate the latter approach. The role of myofascial pain in endometriosis has been highlighted[13], and could explain standard medical and surgical treatment failure in some patients. By targeting pelvic myofascial trigger points, the nociceptive sensitization feed-back loop could be interrupted. SWT should be considered as it proved successful in

musculoskeletal diseases with a favourable tolerance profile[14][15][16][17][18][19]. Good outcomes have also been achieved in chronic pelvic pain syndrome/chronic prostatitis in males[20] [21].

RESEARCH OBJECTIVE

To evaluate the feasibility of a prospective, single-blinded, randomized, controlled trial of transvaginal low intensity SWT as a treatment for endometriosis.

METHODS

Study setting

Monocentric (private hospital in Fort-de-France, Martinique, French West Indies).

Eligibility criteria

Inclusion criteria

Women aged 18 years and older, with clinical symptoms and imaging findings on ultrasound scan and MRI confirming the diagnosis of endometriosis. Ovarian endometriomas, deep endometriosis and adenomyosis meet the inclusion criteria. Histological confirmation is not mandatory. Medical treatment (oral progestatives or oestro-progestatives, GnRH analogs, progestin-releasing IUDs) should be deemed unsatisfactory thus warranting the intervention but should not be discontinued during the trial. Pain-relief medication can be prescribed as recommended by standard of care practice.

Exclusion criteria

Women unable to give consent, to understand written and oral French, or to comply with follow-up.

Virgin women.

Women with ongoing uro-genital infection.

Pregnant women (a pregnancy test should be performed 72 hours at least before each session).

Women undergoing fertility treatment.

History of segmental rectal resection with mechanical anastomosis, shaving or discoid resection.

Women with ureterohydrephrosis warranting ureteral stenting and surgical treatment.

History of another pelvic surgery in the last 6 months.

ESSURE tubal contraceptive implants.

Baseline characteristics

Age (< 30, 30-45, > 45 years), Body Mass Index (BMI) (< 18, 18-25, 25-30, > 30), baseline pain level (VAS < 5, 5-7, > 7), menstrual cycle pattern (complete induced amenorrhea, irregular cycle pattern, regular cycle), history of surgery for endometriosis, history of infertility treatment or assisted reproductive technology (ART), parity (para 0, para 1, para 2 or more), ongoing treatment (oral progestatives or oestro-progestatives, GnRH analogs, progestin-releasing IUDs).

Sample size

We aim to recruit 30 patients in each group, according to Browne's recommendations for sample size of pilot trials[22]. The results of this study will facilitate the calculation of an appropriate sample size for further randomized clinical trials.

Randomization

Patients will be allocated to the two groups in a 1:1 ratio using block randomization with a computer-generated list of random numbers using block sizes of four.

Consent

All participants will be given clear oral and written information about the trial and will give written consent. Consent can be withdrawn at any moment.

Authorization

The protocol will be submitted to the regional research ethical committee (*comité de protection des personnes CPP Sud-Ouest et Outre-Mer III, Bordeaux*).

Intervention

Transvaginal low intensity SWT will be applied on a weekly basis for 4 weeks, using a Masterpuls® One system with a Sparrow® handpiece (Storz Medical, Switzerland). Each session will consist of a systematic application of radial shockwaves at the level of the cervix, at the mid vaginal level and at the lower vaginal level. Targeted applications will be directed to the vaginal fornices or vaginal walls depending on the identified lesions (i.e. posterior vaginal fornice in case of a posterior nodule) and trigger point localization by the probe pressure (at each level : 2 bars, 720 pulses, 5 Hz, 2 minutes). A sham procedure will be carried out in the control group (blinded to the patient only). The typical sound signature of SWT should be maintained during the sham procedure.

Assessment

Clinical evaluation will be carried before treatment, at 1 month, 3 months and 6 months using validated questionnaires.

Primary endpoint : Pain level (Visal Analog Scale) in dysmenorrhea and chronic pelvic pain.

Secondary endpoints

Quality of life (French version of EHP-5[23]).

Digestive symptoms (French version of Kess questionnaire[24]).

Urinary symptoms (USP questionnaire[25]).

Sexual function (French version of FSFI questionnaire[26])

Use of pain relief medication (type and frequency per week)

Tolerance will be assessed by the analysis of adverse events (pelvic, vulvo-vaginal, urinary, digestive or other events).

Statistical analysis

Analysis will be carried out on an intention-to-treat (ITT) basis and will be performed using SPSS 23.0 statistical software (IBM SPSS Statistics, New York, USA). The distributed variables will be compared by using the student t test. Statistical analysis of continuous values will be carried through the independent samples *t* test. The Mann–Whitney *U* test and the χ^2 test will be used for the comparison of quantitative data. $P<.05$ will be considered statistically significant.

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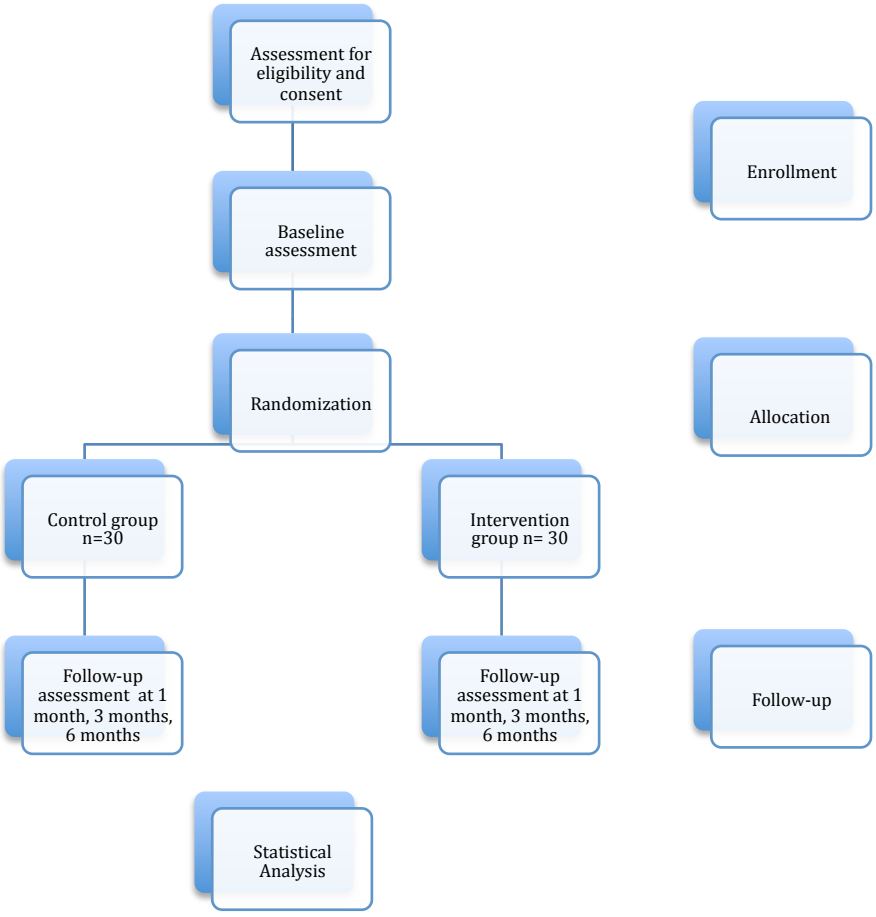
DISCUSSION

Efficacy and safety of SWT as a treatment for endometriosis have yet to be demonstrated. We believe a pilot human trial is ethically and scientifically acceptable, without prior animal experimentation, as this technique is widely used in other indications worldwide in standard clinical settings. The goal is primarily to validate the feasibility of a future larger trial by assessing tolerability, randomization acceptance and implementation, follow-up and evaluation. Although probably underpowered to detect a small difference between the two groups, collected data will help with future study designs (for exemple to determin sample sizes). Subgroup analysis will obviously need larger trials (comparison between DIE, adenomyosis and ovarian endometrioma groups, comparaison between different hormone therapy groups etc.). Technically, the choice of low intensity (equivalent to 0,09 $mJ/mm^{2)}$ and radial shockwaves aims to maximize tolerability and safety (no systematic anesthesia requirement). The larger biological effect cone of radial shockwaves versus focalized shockwaves can be seen as an asset, as ultraprecise targeting is not required.

Ultrasound targeting of endometrial lesions is possible but remains operator-dependent, time-consuming and increases costs. Radial SWT yelded the same results as focalized SWT in the treatment of muscle spasticity after stroke[18]. Further evaluation of energy intensities and focalization is needed. In a trial of focused SWT in myofascial pain, both high and low intensity treatment regimens had good outcomes, albeit with superior functional improvement in the high intensity group[15]. Other questions include the number of optimal repeat procedures, the role of SWT before surgery and ART, and fertility outcomes.

FLOW CHART



The authors do not declare any conflict of interest.

BIBLIOGRAPHY

[1] P. Parasar, P. Ozcan, K.L. Terry, Endometriosis: Epidemiology, Diagnosis and Clinical Management, Curr. Obstet. Gynecol. Rep. 6 (2017) 34–41. https://doi.org/10.1007/s13669-017-0187-1.

[2] C.M. Becker, W.T. Gattrell, K. Gude, S.S. Singh, Reevaluating response and failure of medical treatment of endometriosis: a systematic review, Fertil. Steril. 108 (2017) 125–136. https://doi.org/10.1016/j.fertnstert.2017.05.004.

[3] C.D. Cicco, R. Corona, R. Schonman, K. Mailova, A. Ussia, P.R. Koninckx, Bowel resection for deep endometriosis: a systematic review, BJOG Int. J. Obstet. Gynaecol. 118 (2011) 285–291. https://doi.org/10.1111/j.1471-0528.2010.02744.x.

[4] G. Dubernard, R. Rouzier, E. David-Montefiore, M. Bazot, E. Daraï, Urinary complications after surgery for posterior deep infiltrating endometriosis are related to the extent of dissection and to uterosacral ligaments resection, J. Minim. Invasive Gynecol. 15 (2008) 235–240. https://doi.org/10.1016/j.jmig.2007.10.009.

[5] H. Roman, M. Vassilieff, J.J. Tuech, E. Huet, G. Savoye, L. Marpeau, L. Puscasiu, Postoperative digestive function after radical versus conservative surgical philosophy for deep endometriosis infiltrating the rectum, Fertil. Steril. 99 (2013) 1695–1704. https://doi.org/10.1016/j.fertnstert.2013.01.131.

[6] G. Carrafiello, F. Fontana, C. Pellegrino, M. Mangini, L. Cabrini, D. Mariani, F. Piacentino, S. Cuffari, D. Laganà, C. Fugazzola, Radiofrequency ablation of abdominal wall endometrioma, Cardiovasc. Intervent. Radiol. 32 (2009) 1300–1303. https://doi.org/10.1007/s00270-008-9500-8.

[7] E. Ryo, S. Takeshita, M. Shiba, T. Ayabe, Radiofrequency ablation for cystic adenomyosis: a case report, J. Reprod. Med. 51 (2006) 427–430.

[8] S. Scarperi, G. Pontrelli, C. Campana, M. Steinkasserer, A. Ercoli, L. Minelli, V. Bergamini, M. Ceccaroni, Laparoscopic Radiofrequency Thermal Ablation for Uterine Adenomyosis, JSLS. 19 (2015). https://doi.org/10.4293/JSLS.2015.00071.

[9] Q. Guo, F. Xu, Z. Ding, P. Li, X. Wang, B. Gao, High intensity focused ultrasound treatment of adenomyosis: a comparative study, Int. J. Hyperth. Off. J. Eur. Soc.

Hyperthermic Oncol. North Am. Hyperth. Group. (2018) 1–5. https://doi.org/10.1080/02656736.2018.1509238.

[10] L. Zhao, Y. Deng, Q. Wei, J. Chen, C. Zhao, Comparison of ultrasound-guided high-intensity focused ultrasound ablation and surgery for abdominal wall endometriosis, Int. J. Hyperth. Off. J. Eur. Soc. Hyperthermic Oncol. North Am. Hyperth. Group. (2018) 1–6. https://doi.org/10.1080/02656736.2018.1511836.

[11] G. Dubernard, A. Gelet, C. Lafon, N. Guillen, F. Chavrier, J.-Y. Chapelon, C. Huissoud, C.-A. Philip, Transrectal high-intensity focused ultrasound as focal therapy for posterior deep infiltrating endometriosis, Ultrasound Obstet. Gynecol. Off. J. Int. Soc. Ultrasound Obstet. Gynecol. 51 (2018) 145–146. https://doi.org/10.1002/uog.17497.

[12] E. Melki, Endometriosis treatment with shock waves: A novel approach, Med. Hypotheses. 124 (2019) 114–117. https://doi.org/10.1016/j.mehy.2019.02.022.

[13] J.V. Aredo, K.J. Heyrana, B.I. Karp, J.P. Shah, P. Stratton, Relating Chronic Pelvic Pain and Endometriosis to Signs of Sensitization and Myofascial Pain and Dysfunction, Semin. Reprod. Med. 35 (2017) 88–97. https://doi.org/10.1055/s-0036-1597123.

[14] Ö. Gesginaslan, S. Gümüs Atalay, High-Energy Flux Density Extracorporeal Shock Wave Therapy Versus Traditional Physical Therapy Modalities in Myofascial Pain Syndrome: A Randomized-controlled, Single-Blind Trial, Arch. Rheumatol. 35 (2019) 78–89. https://doi.org/10.5606/ArchRheumatol.2020.7496.

[15] K.D. Park, W.Y. Lee, M. Park, J.K. Ahn, Y. Park, High- versus low-energy extracorporeal shock-wave therapy for myofascial pain syndrome of upper trapezius, Medicine (Baltimore). 97 (2018). https://doi.org/10.1097/MD.0000000000011432.

[16] B. Eftekharsadat, N. Fasaie, D. Golalizadeh, A. Babaei-Ghazani, F. Jahanjou, Y. Eslampoor, N. Dolatkhah, Comparison of efficacy of corticosteroid injection versus extracorporeal shock wave therapy on inferior trigger points in the quadratus lumborum muscle: a randomized clinical trial, BMC Musculoskelet. Disord. 21 (2020). https://doi.org/10.1186/s12891-020-03714-3.

[17] S. Aktürk, A. Kaya, D. Çetintaş, G. Akgöl, A. Gülkesen, G.A. Kal, T. Güçer, Comparision of the effectiveness of ESWT and ultrasound treatments in myofascial pain syndrome: randomized, sham-controlled study, J. Phys. Ther. Sci. 30 (2018) 448–453. https://doi.org/10.1589/jpts.30.448.

[18] Y.-T. Wu, C.-N. Chang, Y.-M. Chen, G.-C. Hu, Comparison of the effect of focused and radial extracorporeal shock waves on spastic equinus in patients with stroke: a randomized controlled trial, Eur. J. Phys. Rehabil. Med. 54 (2018) 518–525. https://doi.org/10.23736/S1973-9087.17.04801-8.

[19] K. Walewicz, J. Taradaj, M. Dobrzyński, M. Sopel, M. Kowal, K. Ptaszkowski, R. Dymarek, Effect of Radial Extracorporeal Shock Wave Therapy on Pain Intensity, Functional Efficiency, and Postural Control Parameters in Patients with Chronic Low Back Pain: A Randomized Clinical Trial, J. Clin. Med. 9 (2020). https://doi.org/10.3390/jcm9020568.

[20] B. Vahdatpour, F. Alizadeh, A. Moayednia, M. Emadi, M.H. Khorami, S. Haghdani, Efficacy of extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome: a randomized, controlled trial, ISRN Urol. 2013 (2013) 972601. https://doi.org/10.1155/2013/972601.

[21] Z.-X. Zhang, D. Zhang, X.-T. Yu, Y.-W. Ma, Efficacy of Radial Extracorporeal Shock Wave Therapy for Chronic Pelvic Pain Syndrome: A Nonrandomized Controlled Trial, Am. J. Mens Health. (2018) 1557988318814663. https://doi.org/10.1177/1557988318814663.

[22] R.H. Browne, On the use of a pilot sample for sample size determination, Stat. Med. 14 (1995) 1933–1940. https://doi.org/10.1002/sim.4780141709.

[23] F. Renouvel, A. Fauconnier, H. Pilkington, P. Panel, [Linguistic adaptation of the endometriosis health profile 5: EHP 5], J. Gynecol. Obstet. Biol. Reprod. (Paris). 38 (2009) 404–410. https://doi.org/10.1016/j.jgyn.2009.05.003.

[24] SNFCP, GFNG, SNFGE, Recommandations pour la pratique clinique de la prise en charge de la constipation (www.snfcp.org/recommandations), (2017). https://www.snfcp.org/recommandations/.

[25] F. Haab, F. Richard, G. Amarenco, P. Coloby, B. Arnould, K. Benmedjahed, I. Guillemin, P. Grise, Comprehensive evaluation of bladder and urethral dysfunction symptoms: development and psychometric validation of the Urinary Symptom Profile (USP) questionnaire, Urology. 71 (2008) 646–656. https://doi.org/10.1016/j.urology.2007.11.100.

[26] S. Wylomanski, R. Bouquin, H.-J. Philippe, Y. Poulin, M. Hanf, B. Dréno, R. Rouzier, G. Quéreux, Psychometric properties of the French Female Sexual Function Index (FSFI), Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabil. 23 (2014) 2079–2087. https://doi.org/10.1007/s11136-014-0652-5.