












Clinical Efficacy of Multi-Focal Low-Intensity Extracorporeal Shockwave Therapy in the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome: Prospective-Randomized, Double Blind, Placebo-Controlled Study

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Purpose: To assess the safety and effect of the multifocal low-intensity extracorporeal shockwave therapy (MESWT) in the treatment of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

Materials and Methods: We randomly separated 30 patients with CP/CPPS into a MESWT and placebo group of same number using prospective-randomized, double-blind design. The participants' National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) total and subdomain scores, International Prostate Symptom Score (IPSS), International Index of Erectile Function-5 (IIEF-5), and visual analogue scale (VAS) were assessed and compared at baseline and at finishing immediately and 4 weeks after procedure and also were compared between MESWT and placebo group.

Results: A total of 30 participants were randomized a MESWT or placebo group. Twenty of thirty participants completed this trial. NIH-CPSI total and subdomain scores, IPSS, IIEF-5, and VAS had significantly ameliorated compared with baseline in the MESWT group at 4 weeks assessment. Furthermore, comparison of the results from MESWT and placebo groups represented statistically significant differences in NIH-CPSI total and subdomain scores, IPSS, IIEF-5, and VAS. No side effects or events were occurred in both groups of the participants during study periods.

Conclusions: MESWT can be an effective treatment modality in patients with CP/CPPS as it improves pain and QoL.

Keywords: Chronic pelvic pain syndrome; Low-intensity extracorporeal shock wave therapy; Multi-focal

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INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a frequent urologic disease in male [1,2]. National Institutes of Health (NIH) category III CP/CPPS is the most common subtype of prostatitis, with a heterogenous and mainly uncertain causes. Inflammatory and non-inflammatory CP/CPPS is distinguished according to clinical presentation of patients, the absence or presence of white blood cells or bacteria in the expressed prostate secretion (EPS), post prostatic massage urine or seminal fluid [3,4]. The major symptoms of this disease contain persistent and recurrent pelvic floor, lower abdomen, perineum, scrotum and penis pain and discomfort, various degrees of lower urinary tract symptoms such as dysuria, frequency, urgency and sense of incomplete urination.

Many studies represented that CP/CPPS III patients have been suffered for a long time without a treatment. Furthermore, there is no standard therapy of CP/CPPS until a recent date [5,6]. Various treatment options are suggested, like antibiotics, non-steroidal anti-inflammatory agents, α -blocker, and non-medical modalities (electromagnetic therapy, physiotherapy, neuromodulatory therapy, intraprostatic injection, and transcutaneous electrical nerve stimulation). However, any of these therapy modalities did not reveal significant success rate [2,7,8].

Several studies have recently reported the effectiveness and safety of low-intensity extracorporeal shock wave therapy (Li-ESWT) for patients with CP/CPPS [9-12]. However, these studies almost utilized uni-focal ESWT for the treatment of CP/CPPS. Recently, multi-focal low-intensity extracorporeal shock wave therapy (MESWT) was invented and manufactured in Korea. The main feature of MESWT is that the treatment effect can be increased by expanding the shockwave therapy zone. To our knowledge, there was no study to evaluate the efficacy and safety MESWT for the treatment of CP/CPPS. This present study uses randomized controlled design in order to assess the exact effect of MESWT on the clinical effectiveness and safety of CP/CPPS.

MATERIALS AND METHODS

1. Study design

This prospective-randomized, double blind, placebo-

controlled study was performed between December 2019 and November 2021 with regard to the ethical guidelines of the Declaration of Helsinki and all International Conference on Harmonization Good Clinical Practice guidelines.

2. Participants

Eligible participants included male 20 years or over with CP/CPPS who show a total NIH-CPSI score >15 . Furthermore, pain or discomfort in the lower abdomen, perineum, scrotum, penis, painful ejaculation, and painful micturition for at least 3 months or more also included in this study. Patients diagnosed with CP/CPPS IIIa and IIIb have been enrolled. CP/CPPS IIIa defined as the presence of white blood cells post-prostatic massage urine. CP/CPPS IIIb defined as patients with pelvic discomfort or pain with absence of infection of post-prostatic massage urine. Patients who correspond to any of the following situation were not included in present study: anatomical abnormalities of the urinary tract, abnormal results of digital rectal examination, prostate specific antigen greater than 4.0 ng/mL, urinary tract infection like urethritis and sexually transmitted disease, history of prostate surgery, urogenital cancer, cardiac pace maker.

3. Treatment and assessment

The treatment was performed with the CENOWAVE (HNT medical, Seoul, Korea) (Fig. 1). This device uses an electromagnetic system to make shockwaves, which are then focused multiple with a parabolic reflector to an energy maximum inside the tissue. The property of this machine is wider treatment area zone compared to existing uni-focal ESWT machine (Fig. 2). Because



Fig. 1. CENOWAVE machine (HNT medical, Seoul, Korea).

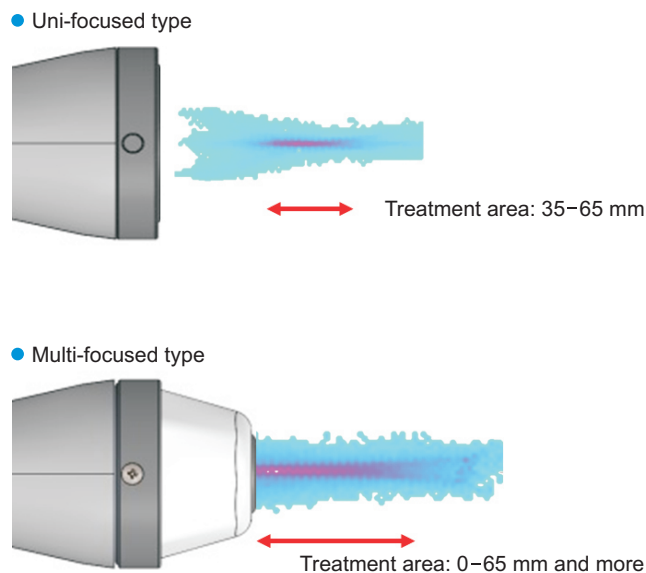


Fig. 2. Comparison of uni-focal and multifocal low-intensity extracorporeal shockwave therapy (MESWT).

the focal zone of MESWT device is spacious, the wide range of shock wave was could be delivered effectively to the entire prostate. The MESWT device was located directly over the skin of perineum at six different areas (500 shocks each region) at every treatment session (Fig. 3). Energy setting was 0.26 mJ/mm^2 for maximal total energy flow density and 3 Hz for frequency. Since research assistants who performed the procedure and investigators are separated, all investigators in the evaluation of the patients were blind to group and procedure assignment. For the placebo group, the same probe with no energy was used. And a similar noise was transferred to participants, which make participants confused whether it is real treatment or not. Participants were assessed physical examination including prostate, vital sign, routine laboratory test, as well as detailed medical history, questionnaires including National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), International Prostate Symptom Score (IPSS), International Index of Erectile Function-5 (IIEF-5), visual analogue scale (VAS). Patients were randomized 1:1 to receive MESWT or placebo once weekly for 8 weeks in an outpatient clinic without any type of anesthesia. Patients were randomized using computer-generated random number tables. Study researcher and participants were not known the procedure assignment. Baseline parameters were evaluated after a two weeks screening duration. All effectiveness assessments were conducted with self-ques-

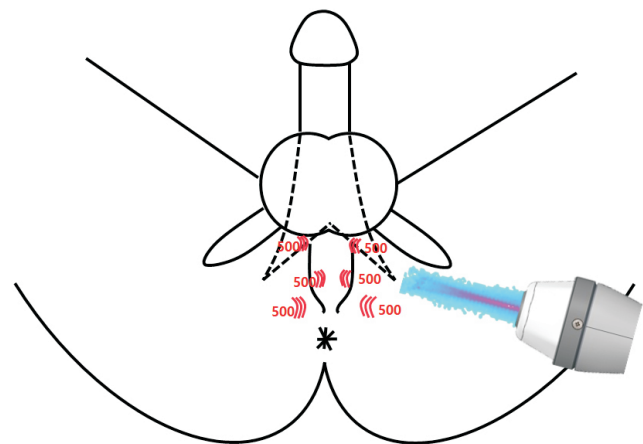


Fig. 3. Treatment of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) using multifocal low-intensity extracorporeal shockwave therapy (MESWT).

tionnaires. Participants made out the NIH-CPSI total and subdomain scores, IPSS, IIEF-5, and VAS at baseline, immediately completing last MESWT procedure and 4 weeks after finishing the MESWT treatment.

The primary end-point was the change from baseline in the total score of NIH-CPSI in MESWT group. Furthermore, secondary end-points included the change in the scores of the IIEF-5, IPSS, and VAS. Adverse events were recorded during the whole period of study.

4. Statistical analysis

Sample size was calculated by 80% power to detect a decreasing of 5 or more score in the total NIH-CPSI score between two groups, using a mean total NIH-CPSI score of 25 and a standard deviation of 5 based on previous study [12]. The sample size of each group was determined to 15 allowing a 20% of drop-out rate. Student's t-test or The Mann–Whitney U-test was used for comparisons in the continuous variables between both groups. The chi-square or Fisher's exact tests were used to compare the qualitative variables. Statistical analysis was executed by SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and p-value <0.05 was considered statistically significant.

5. Ethics statement

The study protocol and amendments was reviewed and approved by an Institutional Review Board of the Seoul St. Mary's Hospital before study starting after obtaining approval by the Korean Ministry of Food and Drug Safety. All participants submit written informed consent when they were enrolled in this trial.

RESULTS

A total of 30 participants observable for the whole follow-up period were enrolled in this trial. Fifteen patients in MESWT group receive multifocal MEWSWT and fifteen patients in the placebo group received placebo ESWT. Twenty-four patients completed procedure and all post-procedure visits. There were 6 patients (2 patients in MESWT, 4 patients in placebo group) who discontinued trial participation owing to drawing voluntarily. The flow chart of present study is depicted in Fig. 4. Baseline demographic characteristics and clinical parameters are represented in Table 1. Mean age of the MESWT group was 53.2 ± 4.7 years and mean age of the placebo group was 51.5 ± 3.1 years. No significant differences in terms of relevant baseline parameters between both groups were shown. There was no significant difference between MESWT group and placebo group in the aspect of total NIH-CPSI score, IPSS, IIEF-5, VAS.

After finishing 8 weeks treatment, NIH-CPSI total scores in MESWT group decreased significantly from baseline (mean difference \pm standard deviation [SD], -9.5 ± 6.0 ; $p < 0.0001$). However, NIH-CPSI total scores in placebo group did not show significant change (mean difference \pm SD, 2.9 ± 5.4). Patients who received MESWT experienced a significant drop in total NIH-CPSI score compared to those who treated placebo ($p < 0.0001$). NIH-CPSI total scores at 4 weeks follow-up after 8 weeks of MESWT group decreased from 26.4 ± 5.7 to 19.9 ± 8.2 , with a difference of 8.3 ($p = 0.0027$). Furthermore, there

was a significantly improvement in the MESWT group compared to placebo group. The voiding domain of the NIH-CPSI improved in MESWT group in finishing treatment immediately follow-up ($p = 0.002$). The improvement in the MESWT group compared to placebo group represented statistically significant in all follow-up duration ($p = 0.0023, 0.0307$). A significant improvement was also observed in pain and quality of life (QoL) domain in the MESWT groups after procedure. A significant overall improvement in the IPSS, IIEF-5, VAS score was represented in the MESWT group. These results represented in Table 2. Amelioration of NIH-CPSI, IPSS, IIEF-5, VAS score in the MESWT group showed both CPPS IIIa and IIIb patients.

No adverse events related with MESWT, like ecchymosis, perineal pain, gross hematuria, hematospermia was not observed in any of the participants.

DISCUSSION

The causes of CP/CPPS are complicated, and its pathogenesis has not been fully explained so far. Although medical therapy does not have a definite treat-

Table 1. Baseline characteristics and clinical parameters of participants

Variable	MESWT group (n=15)	Placebo group (n=15)	p-value
Participants age (y)	53.2 ± 4.7	51.5 ± 3.1	0.718
Height (cm)	172.0 ± 6.7	174.3 ± 5.1	0.295
Body weight (kg)	69.5 ± 8.8	71.5 ± 8.8	0.228
BMI (kg/m^2)	23.5 ± 7.1	23.6 ± 6.2	0.325
PSA (ng/mL)	0.63 ± 0.38	1.25 ± 1.14	0.147
Symptoms duration (mo)	62.7 ± 47.5	34.9 ± 32.5	0.076
Category IIIa/IIIb	11/4	13/2	0.333
NIH-CPSI			
Total score	28.1 ± 6.5	24.7 ± 4.4	0.096
Pain domain score	13.9 ± 2.9	11.8 ± 2.8	0.053
Urinary domain score	4.3 ± 2.7	3.9 ± 1.7	0.634
QoL score	10.0 ± 1.9	9.0 ± 1.9	0.164
IPSS	13.5 ± 8.0	11.9 ± 6.9	0.532
IIEF-5	15.7 ± 12.9	14.9 ± 12.1	0.723
VAS	6.4 ± 1.7	5.7 ± 1.7	0.079

Values are presented as mean \pm standard deviation or number only.

MESWT: multifocal low-intensity extracorporeal shockwave therapy, BMI: body mass index, PSA: prostate specific antigen, NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index, QoL: quality of life, IPSS: International Prostate Symptom Score, IIEF-5: International Index of Erectile function-5, VAS: visual analogue scale.

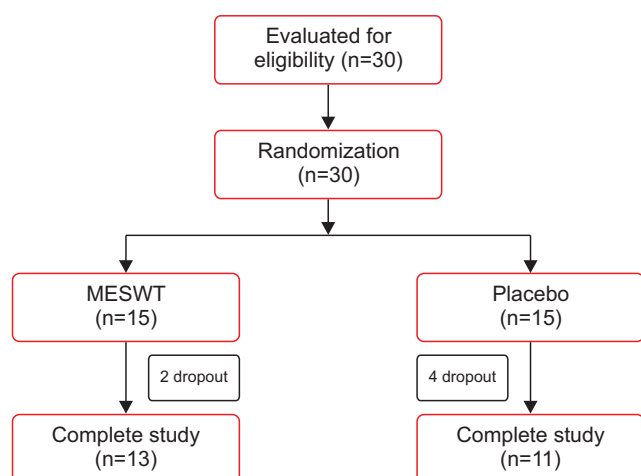


Fig. 4. Flow chart of the study. MESWT: multifocal low-intensity extracorporeal shockwave therapy.

Table 2. Comparison of the baseline and post-treatment results in the MESWT group and placebo group

Outcome	Comparison	Group	Mean±SD	p-value	Comparison	Group	Mean difference±SD	p-value
NIH-CPSI total score	Baseline	MESWT	28.1±6.5	0.096				
		Placebo	24.7±4.4					
	Immediately after treatment	MESWT	18.7±7.5		Baseline vs. immediately after treatment	MESWT	-9.5±6.0	<0.0001
		Placebo	27.5±6.8			Placebo	2.9±5.4	0.047
Pain domain score	1 month after treatment	MESWT	19.9±8.2	0.002	Baseline vs. 1 month after treatment	MESWT	-8.3±8.8	0.003
		Placebo	27.0±4.8			Placebo	2.3±3.5	0.02
	Baseline	MESWT	13.9±2.9					
		Placebo	11.8±2.8					
Urination domain score	Immediately after treatment	MESWT	9.3±3.2	0.001	Baseline vs. immediately after treatment	MESWT	-4.5±2.8	<0.0001
		Placebo	13.9±5.5			Placebo	2.1±4.7	0.07
	1 month after treatment	MESWT	9.8±3.9		Baseline vs. 1 month after treatment	MESWT	-4.1±4.4	0.003
		Placebo	13.3±2.7			Placebo	1.5±2.0	0.008
	Baseline	MESWT	4.3±2.7					
		Placebo	3.9±1.7					
	Immediately after treatment	MESWT	3.1±2.4		Baseline vs. immediately after treatment	MESWT	-1.2±1.2	0.002
		Placebo	4.3±1.6			Placebo	0.4±1.4	0.289
QoL domain score	1 month after treatment	MESWT	3.5±2.8	0.136	Baseline vs. 1 month after treatment	MESWT	-0.8±2.1	0.158
		Placebo	4.6±2.0			Placebo	0.7±1.6	0.094
	Baseline	MESWT	10.0±1.9					
		Placebo	9.0±1.9					
IPSS	Immediately after treatment	MESWT	6.3±2.8	0.001	Baseline vs. immediately after treatment	MESWT	-3.7±2.9	0.001
		Placebo	9.3±1.5			Placebo	0.3±1.1	0.25
	1 month after treatment	MESWT	6.6±2.5		Baseline vs. 1 month after treatment	MESWT	-3.4±3.2	0.001
		Placebo	9.1±1.8			Placebo	0.1±0.7	>0.999
	Baseline	MESWT	13.5±8.0					
		Placebo	11.9±6.9					
	Immediately after treatment	MESWT	9.7±8.5		Baseline vs. immediately after treatment	MESWT	-3.8±2.8	0.001
		Placebo	13.6±6.1			Placebo	1.3±2.35	0.045
IIEF-5	1 month after treatment	MESWT	9.8±8.6	0.046	Baseline vs. 1 month after treatment	MESWT	-3.7±4.5	0.007
		Placebo	13.1±5.5			Placebo	1.13±2.1	0.052
	Baseline	MESWT	15.7±13.0					
		Placebo	15.0±12.1					
	Immediately after treatment	MESWT	24.0±12.7		Baseline vs. immediately after treatment	MESWT	8.33±13.7	0.008
		Placebo	12.7±11.4			Placebo	-2.3±5.3	0.07
	1 month after treatment	MESWT	26.2±10.4		Baseline vs. 1 month after treatment	MESWT	10.5±13.8	0.004
		Placebo	14.0±11.6			Placebo	-0.93±9.1	0.207

Table 2. Continued

Outcome	Comparison	Group	Mean±SD	p-value	Comparison	Group	Mean difference±SD	p-value
VAS score	Baseline	MESWT	6.4±1.7	0.08				
		Placebo	5.7±1.7					
	Immediately after treatment	MESWT	3.7±1.7	<0.001	Baseline vs. immediately after treatment	MESWT	-2.7±1.8	<0.001
		Placebo	6.5±1.6			Placebo	0.8±1.1	
	1 month after treatment	MESWT	3.8±2.1	0.002	Baseline vs. 1 month after treatment	MESWT	-2.6±2.6	0.01
		Placebo	6.7±1.6			Placebo	1.0±1.25	

MESWT: multifocal low-intensity extracorporeal shockwave therapy, SD: standard deviation, NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Index, QoL: quality of life, IPSS: International Prostate Symptom Score, IIEF-5: International Index of Erectile function-5, VAS: visual analogue scale.

ment for CP/CPPS, antibiotics, NSAID, and α blocker are often used for treatment recently. Prostate has several special anatomic features. It is easy to cause local microcirculation interruption owing to wrapping the prostatic inner membrane deeply, the drug is difficult to attain the prostatic lesion due to blocking of drainage [13]. Therefore, it is important to attention to individual treatment and treatment modality options are adopted according to individual clinical manifestations in the treatment of CP/CPPS. While there are many therapeutic options for CP/CPPS, there are no definite and specific treatments, and the results of treatment are unsatisfactory [7]. Since oral medical therapy, most important treatment method for CP/CPPS, have several intractable problems, such as longer treatment duration, higher therapeutic cost, long-term gastrointestinal irritation, this leads to not to sustain treatment and increase to explore new treatment options. Therefore, patients with CP/CPPS underwent long-term medical therapy experience phytotherapeutics such as terpenes, Saw palmetto, quercetin, pollen extract. These phytotherapeutics might be useful treatment modalities since they have few adverse effects [14]. However, there is no scientific evidence supporting these agents, and only few prospective controlled clinical studies have been performed.

Recently, Li-ESWT is used popularly in orthopedics, urology, and plastic surgery. Since Li-ESWT has no or minimal adverse effects, the procedure might be repeated in the patients with refractory other therapeutic modalities. Several mechanism such as decreasing in passive muscle tone, impediment of the flow of nerve impulses, the influence on the neuroplasty of pain memory or hyper stimulation of nociceptors are proposed to the treatment of Li-ESWT for CP/CPPS [9]. Zimmermann et al [10] performed initially prospective randomized control study of the efficacy of ESWT for the treatment of CP/CPPS in 2009. The authors represented that all participants underwent Li-ESWT show a significant improvement in the NIH-CPSI, pain, voiding condition, QoL as compared to the placebo group. A study by Guu et al [15] reported promising results using Li-ESWT in patients who were not treated with a conventional treatment. A total of 33 participants who treated at least 6 weeks using traditional triple therapy including antibiotics, alpha blocker, and a non-steroidal anti-inflammatory drug, were involved in this trial. These patients were experienced a clinically

significant improvement after Li-ESWT therapy. Furthermore, Pajovic et al [12] executed a study to assess the effect of combination of ESWT and triple therapy *versus* triple therapy alone in patients with category IIIb CP/CPPS and showed an increasing effect of adding ESWT to the standard treatment. Patients who were treated triple therapy did not show significant amelioration in post-void residual urine and maximum flow rate; meanwhile, the combination therapy resulted in both significantly improved post-void residual urine and maximum flow rate. All subdomain score of the NIH-CPSI improved statistically significantly in both groups after the therapy, but better results were reported in the group that was treated by the combination of ESWT and triple therapy.

Prospective and randomized present study was designed to assess clinical efficacy in terms of pain decreasing, voiding symptoms, and urinary flow and safety using MESWT in the treatment of CP/CPPS IIIa and IIIb. Administration of MESWT once weekly up to 8 weeks showed a statistically significant and clinically relevant decreasing in symptoms compared with placebo group in patients with CP/CPPS. Almost a 90% positive response was accomplished in the multifocal ESWT group. Notably this present study might be the first MESWT study for CP/CPPS that has revealed significant therapeutic improvement measured by NIH-CPSI total score and the subdomain voiding, pain QoL. Interestingly, although the leukocytes in EPS did not show a decrease in both groups at CP/CPPS IIIa, the improvement of symptoms in MESWT group was accompanied. We think that leukocytes in EPS cannot be correlated with clinical success in this trial. We thought that possible mechanism through which MESWT can improve CPPS may be mediated by anti-inflammatory action. One experimental study reported that LI-ESWT could facilitate downregulation of NF- κ B and NF- κ B dependent inflammatory genes, resulting in positive action on tissue inflammation [16].

However, our present study had several limitations. First, the sample size in this study was small. Secondly, the relative short-term follow-up is also an important limitation. It is mandatory to execute large scale and long-term follow-up study to overcome these limitations. Since there are some differences in the treatment duration according to the reported studies, it is thought that further study is needed to determine the treatment duration. Finally, there was no data that directly

compared the effects of uni-focal ESWT and to those of MESWT. Therefore, our study group plans to perform a study that compares the effect of uni-focal ESWT to that of MESWT in the not too far future.

CONCLUSIONS

Our study results confirmed the efficacy and safety of MESWT in cases of CP/CPPS in the short-term. MESWT is cost-effective, easy to conduct, and prevents side effects. MESWT is a local treatment with the opportunity of repeating the treatment at all time. It is mandatory to perform large-number and long-term follow-up studies comparing the effectiveness of uni-focal ESWT to that of MESWT.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: KSK, SWK. Data curation: KSK, WJB, SWK. Formal analysis: KSK, SWK. Funding acquisition: KSK, SWK. Investigation: KSK, SWK. Methodology: KSK, SWK. Project administration: KSK, SWK. Resources: KSK, SWK. Supervision: YSC, WJB, HJC, USH, SHH, JYL, CHH. Writing – original draft: KSK, SWK. Writing – review & editing: KSK, SWK.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at <https://doi.org/10.7910/DVN/NIYPJG>.

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