Low Intensity Extracorporeal Shock Wave Therapy for Female Stress Urinary Incontinence Using a Vaginal Probe: A Single-Blind, Randomized-Controlled Trial

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המרכז הרפואי שמיר

אוניברסיטת תל-אביב TEL AVIV UNIVERSITY

Background – 1

Low intensity extracorporeal low energy shock wave therapy (LiESWT)

- Clinical LiESWT (2000 to 3000 pulses in 0.20–0.25 mJ/mm2) induces tissue regeneration by:
  - Enhancement of wound healing
  - Promotion of angiogenesis
  - Reduced level of oxidative stress
  - Induction of vascular endothelial growth factor (VEGF) release
  - Proliferation and differentiation of stem cells

- A vast body of evidence has proved LiESWT is effective in treating:
  - Tendon-bone junction diseases,
  - Ischemic cardiovascular disorders
  - Skin wound healing
  - Chronic prostatitis/chronic pelvic pain syndrome (CP/ CPPS)
  - Chronic injuries of soft tissues and
  - Erectile dysfunction

Mouzopoulos et al, Skeletal Radiol. 2007; Yang et al, Heart Vessels. 2013; Wang et al, Int J Surg. 2015; Clavijo et al, J Sex Med. 2017; Zimmermann et al, Eur Urol. 2009

Background – 2

Effect of LiESWT in female LUTS: Pre-clinical studies

Stress urinary incontinence

Sprague–Dawley/Zucker Lean rats
Vaginal balloon dilation-induced SUI

Urodynamic studies:
increased LPP

Immunohistochemical studies:
Promotion of urethral myogenesis
Increased urethral angiogenesis

Wang et al, Neurourol Urodyn. 2018; Wu et al, Transl Androl Urol. 2018; Zhang et al, Urology. 2020

Overactive bladder

Sprague–Dawley rats
Ovariectomy-induced OAB

Urodynamic studies:
significantly improved bladder storage function

Immunohistochemical studies:
improved bladder damages-thicker layer of urothelium
Reduction of interstitial fibrosis

Lin et al, Int J Mol Sci. 2021,

Detrusor underactivity

Sprague–Dawley rats
Streptozotocin-induced DM

Urodynamic studies:
enhanced bladder muscle contractile activity

Immunohistochemical studies:
higher smooth muscle actin expression
recovery of neuronal integrity and innervation

Wang et al, BJU Int. 2018

Background – 3

Effect of LiESWT in female SUI: Clinical studies

Therapeutic effects of Low intensity extracorporeal low energy shock wave therapy (LiESWT) on stress urinary incontinence

Cheng-Yu Long[1,2,3,4,11], Kun-Ling Lin[1,4,11], Yung-Chin Lee[5,6,7], Shu-Mien Chuang[5,8], Jian-He Lu[5,7], Bin-Nan Wu[9], Kuang-Shun Chueh[5,10], Chin-Ru Ker[1], Mei-Chen Shen[5] & Yung-Shun Juan[3,5,7,10*]

- **Single arm, open-label, prospective**
- 50 subjects, SUI with leakage urine ≧2 g on physical activity.
- LiESWT once a week for 8 wks, to the labia minora, 1 month follow-up
- DUOLITH SD1-TOP focused shock wave system (STORZ MEDICAL AG).

Results:

- Significant decrease in leaked urine amount on pad test: 3.60±1.01 ($p<0.01$) and 0.89±0.31 ($p<0.01$)
- Improved functional bladder capacity
- Improved scores on questionnaires: OAB-SS, ICIQ, UDI-6, IIQ-7

- **Multicenter, single-blind, sham-controlled RCT**
- 60 subjects, SUI or SUI-predominant MUI>3 months
- LiESWT once a week for 8 wks, to the labia minora, 6 months follow-up
- DUOLITH SD1-TOP focused shock wave system (STORZ MEDICAL AG).

Results:

- Pad test: No change in sham vs significant in LiESWT. ($p=0.004$)
- Improved scores in ICIQ-SF ($p = 0.034$), UDI-6 ($p = 0.040$), and IIQ-7 ($p = 0.048$), no change in OAB-SS
- 84.5% of patients had >50% improvement at 6 months in study group

SCIENTIFIC REPORTS | (2020) 10:5818 | https://doi.org/10.1038/s41598-020-62471-4

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Objective

The objective of the study was to assess safety and efficacy of LiESWT using a novel ***trans-vaginal probe*** for SUI and sexual function (SF).

Methods – 1

Single-blind, randomized-controlled trial

IRB approval, informed consent

Women with mild to moderate SUI were randomly assigned to

- LiESWT with 0.1 mJ/mm^2 intensity, 1600 pulses, twice weekly for 4 weeks
- LiESWT was delivered for a total of 16 minutes towards 4 points below the urethra, by rotating the probe every 4 minutes by approximately 20 degrees
- Sham treatment, without energy transmission.
- Treatment:sham ratio- 2:1

Both were administered by a vaginal probe (MoreNova^{FEM}, Hikkonu Medical Systems Ltd, Ramat Hasharon, Israel), designed to deliver the pulses towards the peri-urethral tissue

Methods– 2

Inclusion criteria:	Exclusion criteria:
• Age 20-75 • SUI diagnosis according to history and positive cough-stress test • PVR < 50 cc	•Pregnancy or breastfeeding •Severe SUI (1-hour pad test >50 grams) •POP beyond the hymen •MUI with a predominant urgency component (UDI-6 questions 1 or 2 scoring 3 or 4) •History of vaginal fistula; perineal tear grade 4; CPP; GPPPD; genital HSV; active STI; IBD; psychiatric conditions preventing informed consent; therapies affecting bladder function

Methods – 3

Efficacy at 1 month and 6 months post-treatment was evaluated using:

Patient Global Impression of Improvement (PGI-I)

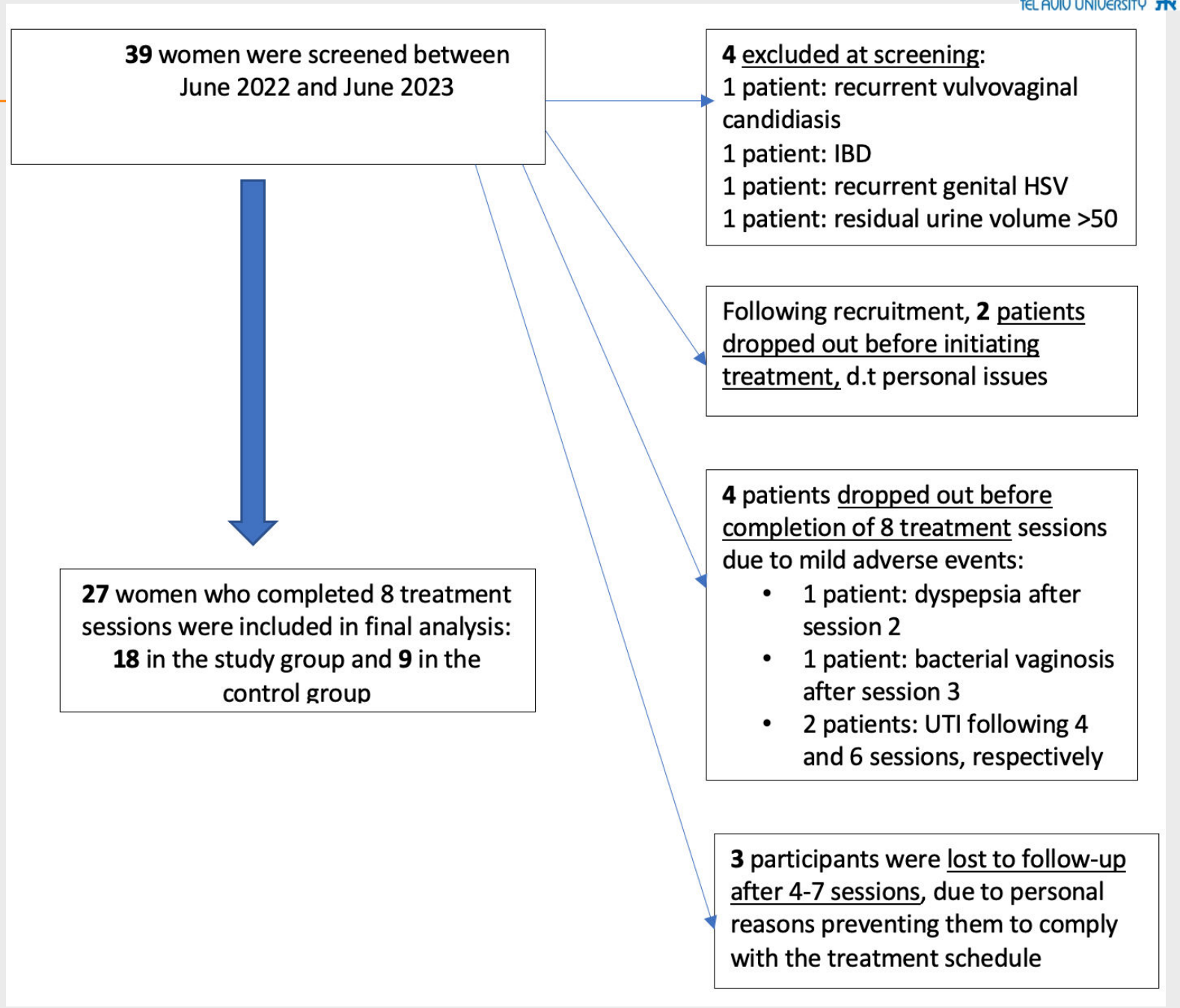
Changes from baseline in scores of:

- International Consultation on Incontinence, Short Form (ICI-Q-SF)
- Urinary Distress Inventory (UDI-6)
- Incontinence Impact Questionnaire (IIQ-7)
- Cough-stress test
- 1-hour pad test.

SF was evaluated by the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR).

Results – 1

Study flowchart



Results – 2

Table 1- Background data

Variables	Sham (N=9)	Treatment (N=18)	P Value
Age (Y)	46.4±9.8	50.1±8.6	0.3404
BMI	27.3±4.4	25.1±3.7	0.1729
Diabetes	0	2 (11.1)	0.1729
Hypertension	2 (22.2)	2 (11.1)	0.5815
Smoking	0	1 (5.6)	1.0000
Parity	3.0 (2.0–3.0)	3.0 (2.0–3.0)	0.8066
Post-menopausal	4 (44.4)	7 (38.9)	1.0000
HRT	0	1 (5.6)	1.0000
Vaginal Estrogen	0	2 (11.1)	0.5385

Pain visual analogue scale (VAS) at treatment n. 8 was 0.6±1.0 and 0.1±0.3, p= 0.2146.

Results – 3

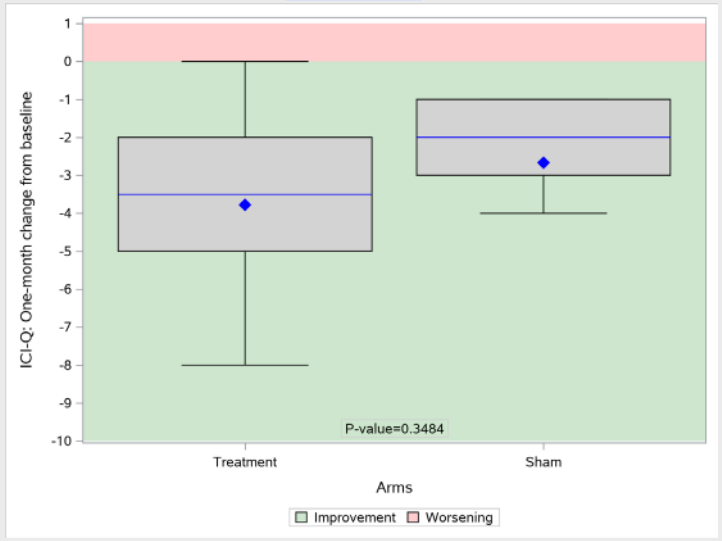
- Both at the 1-month and 6-month follow-up, significantly greater improvement in IIQ-7 scores was observed in the treatment group compared to sham.
- At the 6 month- follow-up, we observed a greater improvement in the one-hour pad test in the treatment group, with borderline statistical significance -1.9±3.8 grams vs. 0.5±3.5 grams, respectively (p=0.055)
- Changes in urinary and sexual function were otherwise similar between groups
- **Possible procedure-related adverse events were mild, and patients fully recovered: spotting (2 women, study group), UTI (1- study group, 1- sham), bacterial vaginosis (1- study group)**

Variables	1-month follow-up			6-months follow-up		
	Sham (N=9)	Treatment (N=18)	P Value	Sham (N=9)	Treatment (N=18)	P Value
cough-stress test status			>0.99			0.657
- No change	6 (66.7)	10 (66.7)		7 (77.8)	9 (64.3)	
- Negative at baseline and positive at follow-up	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
- Positive at baseline and negative at follow-up	3 (33.3)	5 (33.3)		2 (22.2)	5 (35.7)	
change in 1-hour pad test			0.8505			0.0552
Nmiss (%)	1 (11.1)	2 (11.1)		1 (11.1)	4 (22.2)	
Mean±SD	-1.4±4.4	-0.3±3.4		0.5±3.5	-1.9±3.8	
Min–Max	-11.0–4.0	-4.0–11.0		-2.0–9.0	-12.0–6.0	
Median (IQR)	-0.5 (-2.0–0.5)	-1.0 (-1.5–0.0)		-0.5 (-1.0–0.0)	-1.0 (-3.0–-1.0)	
change in ICI-Q			0.3484			0.6448
Mean±SD	-2.7±1.9	-3.8±3.0		-3.1±3.0	-3.6±3.4	
Min–Max	-7.0–-1.0	-11.0–0.0		-9.0–1.0	-11.0–2.0	
Median (IQR)	-2.0 (-3.0–-1.0)	-3.5 (-5.0–-2.0)		-3.0 (-4.0–-1.0)	-4.0 (-6.0–-1.0)	
change in UDI-6			0.9794			0.4997
Mean±SD	-11.9±15.6	-11.2±14.3		-8.7±15.3	-7.1±14.5	
Min–Max	-46.0–5.0	-46.0–8.0		-33.0–25.0	-33.0–25.0	
Median (IQR)	-8.0 (-20.0–0.0)	-10.5 (-17.0–0.0)		-10.0 (-13.0–-5.0)	-8.0 (-16.0–-2.0)	
change in IIQ-7			0.0239			0.0459
Mean±SD	-1.0±7.3	-15.9±25.8		-3.1±9.6	-15.6±23.9	
Min–Max	-10.2–15.0	-100.0–23.9		-19.0–14.6	-95.3–9.6	
Median (IQR)	0.0 (-4.7–0.0)	-12.0 (-19.1–-0.1)		0.0 (-4.7–0.0)	-9.5 (-19.1–-4.8)	
change in PISQ-IR			0.854			0.0644
Nmiss (%)	1 (11.1)	2 (11.1)		1 (11.1)	5 (27.8)	
Mean±SD	0.1±0.3	0.1±0.3		0.2±0.3	0.0±0.2	
Min–Max	-0.4–0.5	-0.7–0.6		-0.2–0.6	-0.3–0.4	
Median (IQR)	0.1 (-0.2–0.4)	0.1 (-0.0–0.2)		0.3 (0.1–0.4)	0.0 (0.0–0.1)	
PGI-I at follow-up			>0.99			>0.99
Improvement (1-2)	1 (14.3)	4 (25.0)		3 (33.3)	5 (29.4)	
No change (3-5)	6 (85.7)	12 (75.0)		6 (66.7)	12 (70.6)	
Worsening (6-7)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

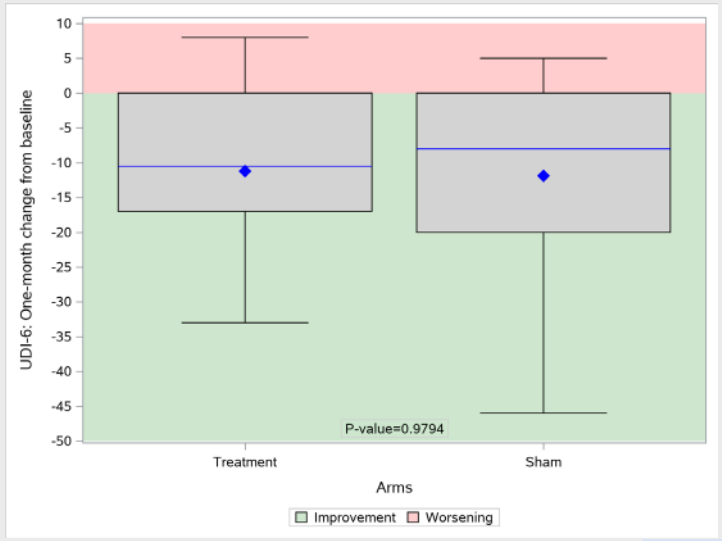
Results – 4

1-month follow-up

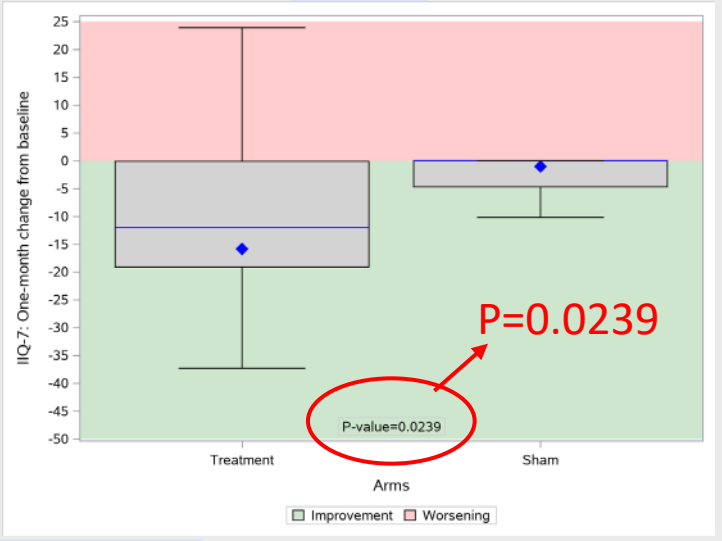
ICI-Q



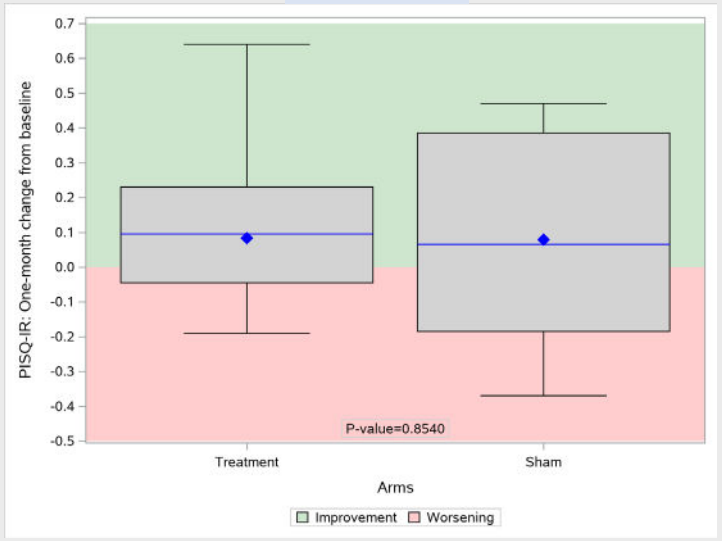
UDI-6



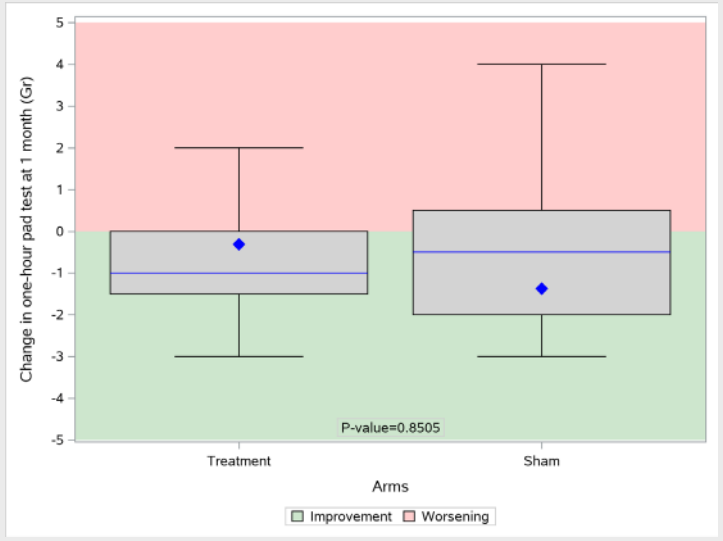
IIQ-7



PISQ-IR



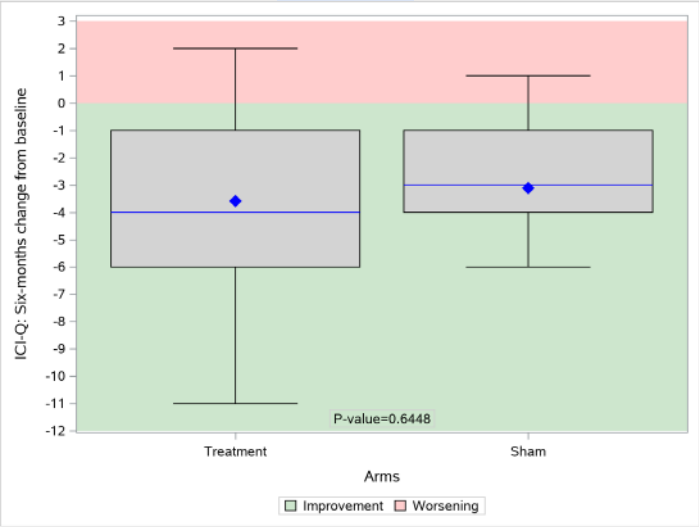
One-hour pad test



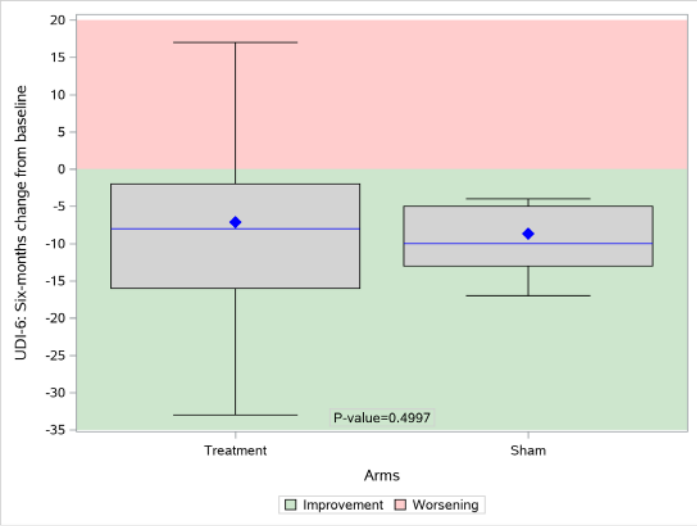
Results – 5

6-month follow-up

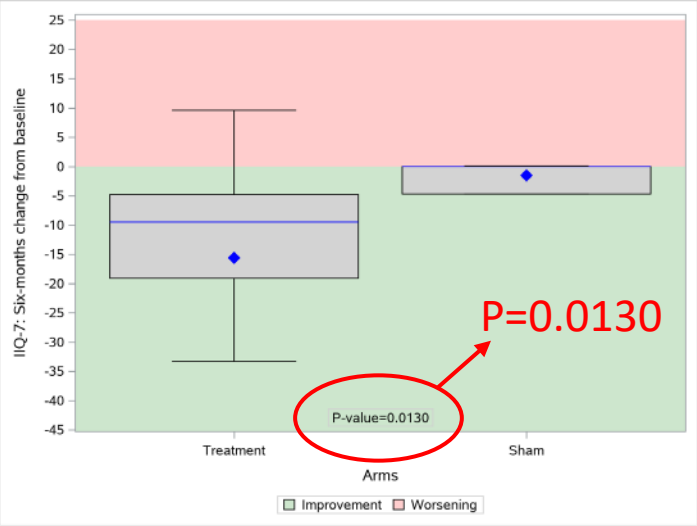
ICI-Q



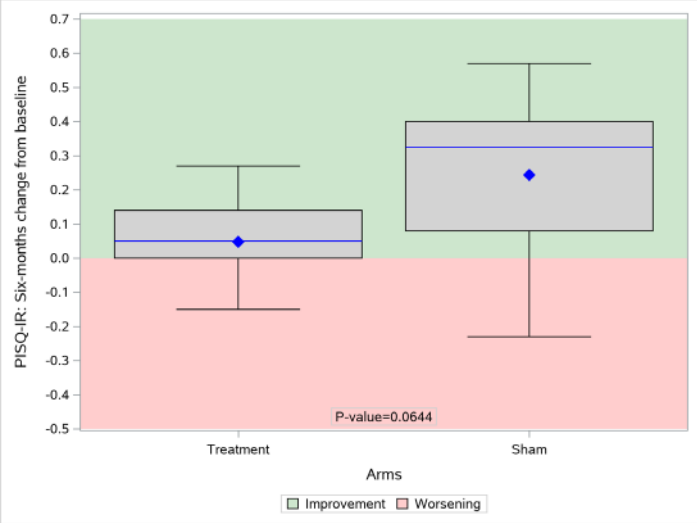
UDI-6



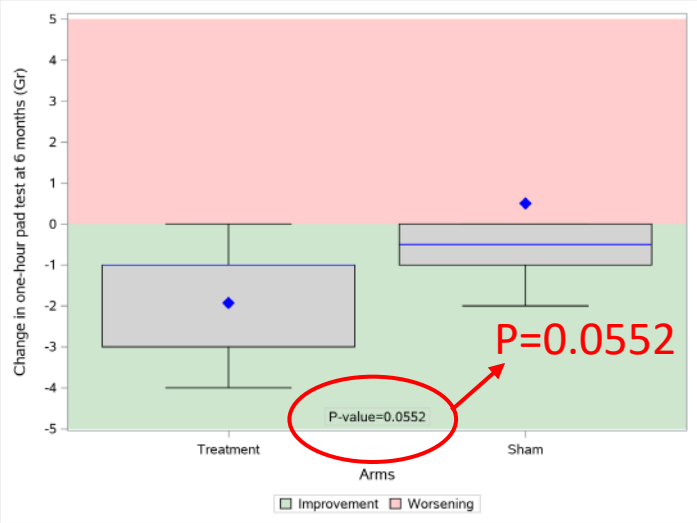
IIQ-7



PISQ-IR



One-hour pad test



Conclusions

We have shown that LiESWT is feasible and well tolerated by women, causing no discomfort or pain

The treatment has proved safe on 6-months follow-up, with few and mild procedure-related adverse events

At the 6-months follow-up, we observed a greater improvement in the amount of urine leakage in the treatment arm, assessed by the 1-hour pad test

We also observed a greater improvement in the impact of SUI on quality of life in the treatment arm 1 month and 6 months following treatment completion, as reflected by a significant decrease in IIQ-7 scores

Acknowledgements

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Thank you for your attention! Questions?