Introduction

Stress urinary incontinence (SUI) is a common and distressing condition.[1, 2] The 5th International Consultation of Incontinence (ICI) advocates pelvic floor muscle training (PFMT) with success rates of 15 to 56% as the gold standard non-surgical treatment.[3-5] However, there is currently no standardized PFMT regimen,[6] and its success is often limited by poor compliance.[7, 8] Other non-surgical options (e.g. biofeedback, vaginal cones and electrical stimulation) are limited by low success rates (9 to 63%), side effects and embarrassment from probe insertion into vagina.[9-11]

In contrast, the gold standard surgical interventions (midurethral slings) have superior success rates of 56 to 98% at 1 year,[12, 13] but Blaivas recently reviewed more than 1000 published studies and reported serious complications defined as those that required further surgery (5.6%) and those that were refractory to treatment (15.3%), and surgical failure of 8% at 5 years post-operatively.[14] In a healthcare database survey in the United States involving 155,458 women who underwent SUI surgery, the 9-year cumulative incidence of repeat surgery was 14.5%.[15] Furthermore, approximately 75,000 federal lawsuits against transvaginal mesh manufacturers in the United States have been reported due to "false and misleading information" about products' effectiveness and safety.[16] Epidemiology study by Coyne et al[17] involving 3934 females with SUI reported presence of co-morbidities such as hypertension (34.3%) and diabetes (9.3%) which may increase risk of surgery. A few cross-sectional surveys on patients' treatment-seeking behaviour reviewed that most patients preferred non-surgical options.[18, 19]

Pulsed magnetic stimulation (PMS) has been used as a non-surgical option for SUI since 1998 due to its established safety, automatic contractions (patients do not need to identify

correct muscles), no discomfort from probe insertion and easy to administer (machine-operated).[20] The 5th ICI emphasized that current evidence is insufficient to guide any recommendation on PMS use for urinary incontinence, and that well-powered randomized controlled trials are needed to study effects of PMS in different diagnostic groups.[3]

Our group first published a systematic review of existing evidence focusing on efficacy of PMS on urinary incontinence.[20] Most of the published studies using PMS on SUI had key limitations including small sample size, lack of a sham arm, non-standardized outcome measures, poor reporting based on the Consolidated Standards of Reporting Trials (CONSORT) statement and short follow-up length.[20, 21] We designed a multicenter, randomized, double-blind, sham-controlled trial to address the limitations noted.[3, 22]

Materials and methods

Study design

The detailed study design has been published previously.[22] Briefly, this study (ClinicalTrials.gov Identifier: NCT01924728) was undertaken in participating hospitals in Penang, Malaysia. The study was approved by Joint Ethics Committee of the School of Pharmaceutical Sciences, USM-HLWE on Clinical Studies [USM-HLWE/IEC/2013(0006)]. All subjects provided written informed consent.

Patient population

Eligible subjects were female aged ≥21 years old, demonstrated urine leak on coughing, had International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI SF) score of ≥6 points and were able to carry out the 1-hour pad test.[22] Subjects were excluded if they had (i) other subtypes of urinary incontinence, (ii) severe cardiac arrhythmia, (iii) cardiac pacemaker, (iv) neurologic conditions (e.g. stroke, epilepsy, Parkinson's disease, multiple sclerosis), (v) pelvic irradiation, (vi) previous surgery for SUI, (vii) previous treatment with PMS, (viii) medication which can affect continence mechanisms, (ix) prolapse stage III or IV, (x) severe urethral sphincter weakness/defect or urethral/vesical fistula, (xi) post void residual volume greater than 200ml or (xii) pregnant.

Intervention and randomization

The device utilized was QRS-1010 PelviCenter (QRS-International, Liechtenstein) which uses PMS for pelvic floor muscle stimulation. A total of 120 eligible subjects were recruited and assigned 1:1 to either active or sham PMS using computer-generated, permuted block randomization (Fig. 1). The treatment regimen involved 2 sessions per week for 2 months (16 sessions, 20 minutes each), administered by one of the trained nurses not involved in subjects'

assessments. After 2 months, subjects who were non-responder or not satisfied with their treatment response could opt for 16 additional active PMS sessions (open-label phase). Subjects were divided into one of the four arms as follow:

- Code 0: 'Sham + no additional PMS' (Total: 0 active session)
- Code 1: 'Sham + additional PMS' (Total: 16 active sessions)
- Code 2: 'Active + no additional PMS' (Total: 16 active sessions)
- Code 3: 'Active + additional PMS' (Total: 32 active sessions)

Follow-ups were conducted at months 5, 8 and 14.

Study measures

Baseline assessments included demographic data, medical history, examination for prolapse, urine analysis, urine pregnancy test, ultrasound and uroflowmetry with post-void residual volume.

The primary response criterion was a 5-point reduction in the ICIQ-UI SF score (range 0-21).[23] The secondary outcome measures included: (i) objective cure (leakage of less than 1 gram on 1-hour pad test); (ii) subjective cure ('never' response to question 'How often do you leak urine?' i.e. question 3 of ICIQ-UI SF); (iii) incontinence episode frequency; (iv) 1-hour pad test; (v) pelvic floor muscle function; (vi) incontinence severity improvement in ICIQ-UI SF category; (vii) Patient Global Impression of Improvement (PGI-I) and (vii) International Consultation on Incontinence Questionnaire-Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol) (range: 19-76).

Statistical analysis

Setting two-sided significance level at 0.05 with 80% power, 120 subjects were required, assuming 60% response in active and 30% in sham arms with 25% attrition.[22] Data was analysed according to an 'intention-to-treat' principle. For univariate analysis, chi-square test was used for responder analysis at individual time points. For multivariate analysis, data were analyzed by a longitudinal method using linear mixed model (LMM) for continuous variables and generalized linear mixed model (GLMM) for dichotomous variables. For responder analysis, subjects who withdrew after randomization were considered as treatment failures and were included in the denominator. Statistical analyses were conducted by an independent statistician not involved in patients' assessment.

Results

Initial response rates (at 2 months)

From September 2013 to March 2015, 168 subjects were screened to enroll 120 subjects (Fig. 1). The active and sham arms were not significantly different in baseline demographic characteristics and outcome measures (Table 1).

Using the primary criterion for response (≥5 point reduction in the ICIQ-UI SF score), 45 of 60 subjects (75.0%) in the active and 13 of 60 subjects (21.7%) in the sham arms were treatment responders (relative risk 3.46, 95% CI 2.09-5.72, $p<0.001$) (Table 2). The responder rates of the key secondary criteria (objective and subjective cure), incontinence episode frequency, 1-hour pad test, incontinence severity and Patient Global Impression of Improvement (PGI-I) were significantly different between the active and sham arms after one and two months of treatment ($p<0.05$) (Table 2).

In assessment of blinding, 26 (46%) active and 38 (66%) sham subjects thought that they received active PMS, while 28 (49%) active and 16 (28%) sham subjects responded 'don't know' ($p=0.06$, chi-square test). Of all evaluable subjects, 3 (5.3%) of 57 subjects in the active and 5 (8.6%) of 58 subjects in the sham arms experienced adverse events ($p=0.72$, Fisher's exact test). These events included pain at gluteal muscles and hipbone, yellow vaginal discharge, constipation, diarrhea, mouth ulcer, delayed menstruation, burning sensation or difficulty in passing urine. All uroflowmetry parameters were not significantly different between the treatment arms ($p>0.05$).

Long term response rates (at 14 months)

Of the 120 subjects enrolled, 24 (40%) subjects from the active and 41 (68%) from the sham arms opted for additional active PMS sessions (Fig. 1). A total of 106 (23 in 'active + additional PMS', 31 in 'active + no additional PMS', 40 in 'sham + additional PMS' and 12 in 'sham + no additional PMS' arms) completed follow-up at 14 months.

Primary outcome

Responder analysis

Using the primary criterion for response, subjects who received 32 sessions of active PMS (Code 3) had the highest percentage of treatment responders (n=18/24, 75.0%) (Table 3). Regardless of number of PMS sessions (16 or 32 sessions), subjects who received active PMS were more likely to be treatment responders compared with subjects who did not receive any active PMS (0 active session) (p<0.001).

Analysis of continuous outcome data

Subjects who received active PMS had statistically significantly higher reduction in the total ICIQ-UI SF total score (Code 1: M_{diff}= -5.63, SE=0.73, Code 2: M_{diff}= -7.13, SE=0.80, Code 3: M_{diff}= -6.80, SE=0.95) compared with subjects who received only sham PMS (M_{diff}= -3.46, SE=1.21) (Table 4, Fig. 2).

Secondary outcomes

Responder analysis

The responder rates of the key secondary criteria (objective and subjective cure), incontinence episode frequency, 1-hour pad test, incontinence severity and Patient Global Impression of Improvement (PGI-I) were statistically significantly different for subjects who

received active PMS (Code 1, 2 and 3) versus subjects who received only sham PMS (Code 0) ($p<0.05$) (Table 3). Subjects who received 32 sessions of active PMS (Code 3) had lower objective and subjective cure rates but similar percentage of PGI-I improvement (subjects felt 'much better' or 'very much better'), compared with subjects who received only 16 sessions of active PMS (Code 1 and 2).

Analysis of continuous outcome data

There were significant differences between treatment arms who received active PMS (16 or 32 sessions) compared with subjects who received only sham PMS in most secondary outcome measures (Table 4, Fig 3).

Discussion

We conducted a randomized, double-blind, sham-controlled trial with well-powered sample size estimates, included validated measures with minimal clinically important difference (MCID) and reported our paper according to the CONSORT statement.[21] Additionally, we presented our data taking into account both binary outcomes ('responder' or 'non-responder') which can be perceived intuitively as a more relevant information to clinicians and patients to aid in clinical decision-making (Table 2 and 3), and continuous outcomes which prevent data loss from dichotomization (Table 4, Fig. 2 and 3).

The initial results at 2 months suggested that active PMS improved patients' symptoms significantly compared with sham PMS in female patients with SUI. During an additional 1-year of follow-up (at 14 months), the findings suggested that such benefits were sustained over time. Regardless of initial randomization, the active PMS-treated subjects were more likely to have long-term response compared with subjects treated with only sham PMS. Interestingly, subjects who had 32 PMS sessions showed a lower percentage of objective and subjective cure rates than those who had 16 sessions. A possible explanation could be that subjects who had 32 PMS sessions had significantly higher baseline ICIQ-UI SF scores (11.67 ± 3.42) compared with patients who had 16 PMS sessions (9.61 ± 3.35 and 8.78 ± 2.23), indicating higher incontinence severity in the former group. The open-label, non-randomized nature of the study after the initial 2-month treatment could have results in the heterogeneous baseline scores.

We chose the ICIQ-UI SF, a highly recommended questionnaire by 5th ICI, as our primary outcome measure based on the emerging consensus that patient-reported outcomes are the most appropriate when describing treatment success or failure.[24, 25] We further defined our

primary response criterion as a 5-point decrease based on findings from recent studies which determined the MCID of ICIQ-UI SF.[23, 26]

In a recent 2013 randomized study with comparable methodological quality and using the same subjective questionnaire, mean differences in total ICIQ-UI SF scores for adjustable anchored single incision mini-sling and tension-free vaginal tape-obturator sling were -10.43 and -11.65 at 1 year,[27] which showed almost twofold reduction compared with our study (Code 1: M_{diff}= -5.63, Code 2: M_{diff}= -7.13, Code 3: M_{diff}= -6.80). However, it is important to note that approximately 70% of subjects who had active PMS treatments successfully achieved the MCID of 5-point decrease, which was the threshold perceived as clinically meaningful to patients.[23] In contrast, another randomized study using twelve weeks of PFMT with or without biofeedback reported a M_{diff} in total ICIQ-UI SF scores of -3.70 and -3.40, which were below the MCID, and treatment sustainability is not reported.[28] We could not compare our responder rates (≥5-point reduction) with the above two studies that did not define their responder criterion for the ICIQ-UI SF scores.

A 2015 Cochrane review assessing efficacy of midurethral slings at up to 1 year follow-up reported that transobturator slings achieved mean objective and subjective cure of 85.7% and 82.3%, while retropubic slings achieved mean objective and subjective cure of 87.2% and 84.4%.[13] Comparing the two key secondary response criteria, our study showed mean objective (58%) and subjective (37%) cure rates which were about half compared with the Cochrane review. The lower PMS efficacy should be weighed against no surgical risks, no adverse events, no discomfort, no additional risks of co-morbidities, and treatments which are easily reproducible. Several recent Cochrane reviews reported that majority of non-surgical

studies measured their outcomes in non-standardized ways or did not report these treatment outcomes.[9-11] Thus, meaningful comparisons with our study were not possible.

The pelvic floor muscles are a major contributing factor in SUI,[29] and the proposed mechanism of PMS is to increase pelvic floor muscle strength and endurance through repetitive contractions, similar to PFMT. It was thus logical to assess the pelvic floor muscle function changes. At 14 months, subjects who received active PMS sessions showed significantly better pelvic floor muscle function, as measured using perineometer, than subjects who had no active PMS. Furthermore, we showed that 32 PMS sessions resulted in more improvements in maximum and average pelvic floor muscle contractions compared with 16 sessions only.

Our study had a number of strengths. All primary and secondary outcome measures were administered at each follow-up to ensure consistent monitoring in changes in response. Furthermore, the study investigators remained blinded to treatment allocation until unblinding was done at month 14. We employed only validated English, Malay and Chinese questionnaires in our study. We performed blinding assessment and used a valid sham method. The total energy output of 16 sham sessions was 136 kJ (or 8.500J each session), which was far less than the energy output of one 20-minute active mode run (at 100 % intensity) of 408 kJ.

Our study had some limitations. While a comparative study between PMS and PFMT could help better understand the role of PMS in SUI treatment, we opted to conduct a sham-controlled trial which is first needed to confirm its efficacy. Moreover, double-blinding is not possible when comparing PMS and PFMT, which could lead to significant bias. Next, the

high-intensity of the protocol may have limited enrolment. Nevertheless, only 14 (8.3%) eligible subjects refused to participate in our study, which reflects patients' acceptability. Our sample size had adequate power for analyses at two months. The subsequent open-label, non-randomized study resulted in insufficient statistical power. Further study to compare PMS versus PFMT with a long follow-up period and without additional treatments allowed would likely enable a better and statistically powered evaluation of long-term response.

Conclusion

The choice of treatment modalities for SUI should always be based on risk and benefit ratio and patients' personal preference rather than solely on cure or improvement rates. The encouraging long-term response rates, improved pelvic floor muscle function, high patient acceptance, and low dropout rates show that PMS is an attractive and promising non-surgical alternative to patients who do not want to undergo surgery. Studies are indicated to compare PMS with PFMT in a long-term, randomized controlled trial.

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