The Effect of Vaginal Oestriol Cream on Subjective and Objective Symptoms of Stress Urinary Incontinence and Vaginal Atrophy: An International Multi-Centre Pilot Study

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Key Words

Topical oestriol · Stress urinary incontinence · Vaginal atrophy

Abstract

Aim: Subjectively and objectively assess stress urinary incontinence (SUI) symptoms before and after topical oestrogen therapy. **Methods:** A prospective study was performed in 3 centres in South-Africa, Australia and the Netherlands. Postmenopausal women with SUI were treated with topical oestriol cream for 6 weeks. The primary subjective outcome was the Patient's Global Impression of Improvement (PGI-I) scale. The primary objective outcome was vaginal pH. Secondary subjective outcomes were: the International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form, the Incontinence Impact Questionnaire, the Urogenital Distress Inventory (UDI-6) and the most bothersome symptom approach. Secondary objective outcome was the erect cough pad test. Compliance was scored. **Results:** A total of 68 women were enrolled. Half of the participants reported improvement on the PGI-I scale after treatment. Vaginal pH was significantly lower after treatment (median 5.3 (interquartile range (IQR) 4.5–6.0) vs. 5.0 (4.4–5.4), $p = 0.002$).

Improvement on the UDI stress domain was observed ($p = 0.01$). No statistically significant differences were found in the other subjective outcomes. Baseline and repeat cough pad tests demonstrated a wide variation with no significant difference. Compliance was high (median 100 (IQR 83–100)). **Conclusion:** Topical oestriol cream during 6 weeks improved quality of life and vaginal pH but no other objective measures of incontinence.

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Published by S. Karger AG, Basel

Introduction

Urinary incontinence can be classified as stress urinary incontinence (SUI), urge urinary incontinence (UII), and mixed urinary incontinence. SUI is the involuntary loss of urine associated with coughing, sneezing or physical activity. Prevalent in up to 35% of women, it is the most common type of incontinence [1, 2]. Untreated, SUI significantly impacts quality of life causing not only psy-

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chological burden but also financial burden with the daily costs of incontinence material [3].

Different options are available in the treatment of SUI, including pelvic floor muscle training and surgery. Oestrogen has been used to treat incontinence for many decades [4], either alone or in combination with other treatment modalities. Oestrogen plays an important role in the function of the genital and lower urinary tract with oestrogen receptors demonstrated in the vagina, urethra, bladder and pelvic floor musculature [5]. Up to 70% of women relate the onset of urinary incontinence to their final menstrual period [6]. The 2012 Cochrane review regarding oestrogen therapy for urinary incontinence shows that topical oestrogen treatment may improve urinary incontinence [7]. Most of the available evidence regarding proven benefit deals with the symptom of UUI, showing improvement in urgency and bladder capacity [8]. Though topical oestrogen may improve SUI in postmenopausal women, the evidence is limited and must be interpreted with caution due to the small sample sizes and the different types, dosages and durations of oestrogen treatment investigated. The Cochrane review recommends that further research in the form of randomised controlled trials with adequate sample size is recommended [7].

There seems to be a discrepancy between the effect of systemic and topical oestrogens. Where topical oestrogens seem to have a positive effect on urinary incontinence, systemic oestrogen therapy seems to worsen incontinence [7]. Studies have indicated that systemic oestrogen therapy has an effect on collagen remodeling [9–11]. Oestrogen therapy could lead to a reduction in total collagen [9], a decrease in collagen cross linking [10], and an increase in collagen turn-over markers [11]. This combination can lead to a weakened bladder neck support and an increase in the risk of developing stress incontinence. In contrast, topical oestrogens could thicken the urethral mucosa and enhance vascularisation of the periurethral tissues, so theoretically enhancing the 'mucosal seal' [12]. Moreover, subjective improvement of lower urinary tract function with topical oestrogens could be related to the oestrogenic effects reversing the symptoms of vaginal discomfort associated with vaginal atrophy (VA) [13]. These underlying pathophysiologic mechanisms could explain the discrepancy between the effects of systemic and topical oestrogens.

We would like to offer our patients an effective conservative treatment for urinary incontinence. While topical oestrogen is promising in the treatment of SUI, more research is required. We performed a pilot study where UI symptoms were assessed subjectively and objectively at

baseline and after topical oestrogen therapy in combination with subjective and objective assessment of VA to evaluate if indeed topical oestrogens are promising in SUI treatment, and if performing such a study is feasible. Moreover, with this study, we aim to gather preliminary data for a subsequent randomised controlled trial comparing vaginal oestrogen cream with placebo.

Methods

Study Design

A prospective multinational observational pilot study was performed from October 2013 to December 2014 in 3 participating metropolitan centres (Groote Schuur Hospital, Cape Town, South Africa; St. George Hospital, Kogarah NSW, Australia; Academic Medical Centre, Amsterdam, the Netherlands). Written informed consent was obtained prior to enrolment in accordance with the Ethical Committee approval in all 3 centres.

Participants

Postmenopausal women (with their last menstrual period >12 months ago) presenting with a complaint of SUI were asked to participate in the study. Inclusion criteria included a positive response to the question: 'Do you leak urine while coughing, sneezing or while performing any physical activity?' Women with additional symptoms of a pelvic organ prolapse (POP), overactive bladder symptoms or urge incontinence could also be included. Women who had previously used hormone replacement (topical or systemic), who had too little understanding of the common spoken language in the country or who were otherwise unable to provide informed consent were excluded.

Intervention

The current choice of topical oestrogen lies between oestriol (Ovestin) and oestradiol (Vagifem). Since oestradiol is better absorbed systemically and has been shown to promote thickening of the endometrium [14], our departments have traditionally used oestriol, which has poor systemic absorption, yielding serum levels below 90 pmol/l, the traditional cut-off for the 'menopause' status [15]. In our study, patients were treated with oestriol cream 1 mg/g vaginally for 6 weeks. No other treatment for urinary incontinence was allowed. During the first 3 weeks, oestriol cream was used daily with cream administered 3 times per week the next 3 weeks (total 30 applications). Patients were instructed to apply the cream with a finger (the amount equivalent to toothpaste put on a toothbrush) to the opening of the vagina and area between the vaginal opening and urethra. This way, the cream was applied directly on the tissue of interest without the use of the applicator. It has been our experience in all 3 centres that patients (especially the elderly) had difficulty utilising the provided applicator.

Primary Outcomes

The primary subjective outcome was the response to the Patient's Global Impression of Improvement (PGI-I) scale assessed at the follow-up visit. The PGI-I is a 1-item questionnaire with a 7-point Likert scale developed and validated to measure the change of symptoms [16]. The PGI-I response has been shown to correlate

significantly with the frequency of incontinence episodes, cough-test results, pad-test results, and scores on several incontinence quality of life questionnaires [17].

The primary objective outcome was the vaginal pH, which was assessed using a pH strip with a range of pH 4.0–7.0 with intervals of 0.5 (mColorpHast™ strips). Vaginal pH has proven to be an easy and cost-effective method in determining the health of the vaginal epithelium. The decrease in vaginal pH is associated with both reduced symptoms of VA, such as dryness and dyspareunia, and improved cytological condition of the vaginal epithelium [18]. During vaginal examination, the pH strip was placed in the midvaginal position against the posterior vaginal wall for 20 s. The colour change was then compared to a standardised colour chart included with the pH strips 60 s later by the investigator, as previously done by Karp et al. [19] in a randomised clinical trial to assess the effect of vaginal oestrogen on postoperative tissue quality after vaginal reconstructive surgery. The vaginal pH was recorded on a standardised sheet.

Secondary Outcomes

Subjective Outcome Measurements

To assess the subjective outcome, 4 questionnaires were used at both the first and the follow-up visit:

(1) The International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF) has been developed under the auspices of the International Consultation on Incontinence, is easy to complete with low levels of missing data and has shown good validity and reliability [20]. The ICIQ-UI-SF comprises 3 scored items and an unscored self-diagnostic item. It contains 3 components measuring subjective frequency, subjective severity and quality of life. Questions 3–5 are scored items, and the answers are totalled for a minimum score of 0 and maximum score of 21. A significant correlation between the ICIQ-UI-SF and the 24-hour pad test in women with primary SUI has been demonstrated [21].

(2) The Incontinence Impact Questionnaire (IIQ-7) is a disease-specific quality-of-life questionnaire covering the following sections: physical functioning, travel, social functioning and emotional health [22]. A short version of the IIQ, the IIQ-7, has been developed to reduce the respondents' burden [23]. A higher score indicates more impact on daily life of UI. The IIQ-7 has shown to be a reliable, valid, and responsive instrument for assessing the impact on daily life of UI; this also applies for the Dutch version [24].

(3) The Urogenital Distress Inventory (UDI-6) is a standardised questionnaire measuring urogenital symptoms. The questions cover the following 5 sections: urinary incontinence, overactive bladder, pain, obstructive micturition and prolapse. A high score on a particular section means more symptom distress [22]. Again, a short version has been developed [23]. The UDI-6 is divided into 3 domains (irritative, stress and obstructive) and has shown to be a reliable, valid and responsive instrument for assessing symptom distress of urinary incontinence, also in the Dutch population [24].

(4) The most bothersome symptom (MBS) approach is derived from a selected list of symptoms associated with VA (most commonly consisting of the symptoms of vaginal dryness, vaginal itching/irritation and dyspareunia). At baseline, participants are instructed to rate each of these symptoms as not present, mild, moderate or severe and then must select a single symptom among those classified as moderate or severe as the MBS. The MBS is then followed through to the end of treatment, and the change in its severity is used to evaluate symptomatic improvement of VA [25].

Objective Outcome Measurement

At both first and follow-up visit, the standardised cough pad test was performed, which is validated as an alternative to a 24-hour pad test [26]. After confirming >200 ml of urine on bedside bladder ultrasound, the patient received a pre-weighed incontinence pad inserted into the underwear. The patient was then asked to stand and give 3 vigorous coughs while standing. The pad was removed from the underwear, and weighed to an accuracy of 0.1 mg. The weight was recorded on a standardised sheet.

Adherence to Treatment

Participants were asked to use oestriol cream daily for the first 3 weeks, and then 3 times per week from weeks 4–6. Thus, there were 21 + 9 occasions of application, with compliance scored as the percentage of 30 applications. To assess compliance, participants were asked if they had sufficient cream for 6 weeks and if they had experienced trouble to follow the treatment regimen.

Statistical Analysis

The changes in outcome measures after treatment were analysed using the Wilcoxon signed rank test for paired numerical data. Categorical data were expressed as numbers and percentage, not normally distributed numerical data as median with interquartile range (IQR). Total and domain scores of the IIQ-7 and UDI-6 were calculated. In order to examine the relationship between the primary outcome measure (PGI-I) and the other variables, Spearman's correlation coefficients between PGI-I scores and change in outcome measures were analysed.

A p value of <0.05 was considered to be statistically significant. All analyses were performed using the statistical software SPSS version 20.0.

Results

Participants and Baseline Characteristics

A total of 68 women were enrolled with complete data available for 58 women (24 in South-Africa; 25 in Australia; 9 in the Netherlands). The median follow-up was 6.0 (IQR 5.9–6.6) weeks. The main reasons to refuse participation or not complete the follow-up visit included feeling uncomfortable applying local oestrogen cream, experiencing side effects (burning, itching) very shortly after the start of treatment, which led to less than 3 applications or being unable to complete the 6-weeks follow-up visit for personal reasons. Other women were not motivated to participate in this study because they were referred for surgery.

The median age of the participants was 61 (IQR 54.3–66.0) with a median parity of 2 (IQR 2–3). The median body mass index was 27.3 kg/m² (IQR 25.2–30.4). All participants complained of SUI although 68% of patients had mixed incontinence and 51% had concomitant POP.

Fig. 1. PGI-I response.

Fig. 2. Vaginal pH at baseline and after 6 weeks of local oestrogen treatment.

Primary Outcomes

PGI-I Response

Twenty-nine patients (50%) reported improvement after 6 weeks of local oestrogen treatment (fig. 1). In those who did not improve, a majority (41%) reported 'no change' on the 7-point scale. The 2 patients who were re-

ported to be 'very much worse' had both experienced local side effects of the oestriol cream (vaginal burning sensation, vaginal discharge).

Vaginal pH

The vaginal pH was significantly lower after treatment as is demonstrated in figure 2 (median 5.3 (IQR 4.5–6.0) vs. 5.0 (4.4–5.4), $p = 0.002$).

Secondary Outcomes

Subjective Outcome Measurements

ICIQ-UI-SF. Figure 3 shows the pre- and post-treatment ICIQ-UI-SF total scores. The median baseline score was similar to the median score after 6 weeks of local oestrogen treatment with a wider variation in measurements after 6 weeks (13.0 (IQR 10–16) vs. 13.0 (IQR 8–17), $p = 0.27$).

IIQ-7 and UDI-6. A statistically significant reduction in the stress domain of the UDI-6 was observed (median 66.7 (IQR 50.0–83.3) vs. 66.7 (IQR 33.3–83.3), $p = 0.01$). No statistically significant differences were found in the other UDI domain scores, nor in the IIQ total and IIQ domain scores after local oestrogen treatment ($p = 0.21$ – 0.90).

MBS. At baseline, 41% of patients reported no bothersome symptom; after 6 weeks of treatment, this was 38%. Eight patients (14%) that reported one of the symptoms

Fig. 3. ICIQ-IU-SF at baseline and after 6 weeks of local oestrogen treatment.

Table 1. Correlation between PGI-I and change in outcome measures

	Correlation coefficient	p value*
pH	0.01	0.94
Cough pad test	0.03	0.83
ICIQ-UI-SF	0.33	0.01
IIQ total	0.39	0.003
Physical activity	0.25	0.06
Travel	0.39	0.003
Social/relationships	0.40	0.002
Emotional health	0.33	0.01
UDI		
Irritative	0.24	0.08
Stress	0.20	0.15
Obstructive/discomfort	0.20	0.14

* Spearman's correlation coefficient. Bold values in the table are the statistically significant p values <0.05.

as MBS at baseline did not experience this symptom after treatment. In 26%, the reported MBS remained the same and 12% changed their MBS to another symptom after treatment. Nine patients (16%) went from no MBS to reporting one of the symptoms as their MBS after treatment. The most frequently reported MBS was vaginal dryness (22% at baseline, 14% after treatment). The mean severity in MBS increased slightly at the end of treatment compared to baseline (1.72 vs. 1.46 respectively).

Objective Outcome Measurement

Cough pad test. The baseline and 6-weeks follow-up cough pad test demonstrated a wide variation and did not differ significantly (median 5.1 g (IQR 1.0–19.5) vs. 5.3 g (0.2–15.2), $p = 0.66$). A reduction in the amount of urine loss during the pad test was seen in 47% participants; in 43%, the pad weight increased; in 7%, the amount of urine loss remained unchanged.

Adherence to Treatment

Adherence to treatment (scored as the percentage of 30 applications) was high with a median of 100% (IQR 83–100). Data showed 3 participants who overused the cream, from daily use during 6 weeks to 3 times a day for 2–4 weeks. Reasons for non-compliance were side effects like a vaginal burning sensation and/or vaginal itching after application. Other patients forgot several applications or did not feel comfortable applying the cream regularly, for example, because of the fear of side effects.

Adverse Events

Nine women (of the original 68 enrolled) experienced one or more side effects of the oestriol cream like a burning sensation ($n = 4$), vaginal itching ($n = 5$), vaginal bleeding ($n = 1$) and/or vaginal discharge ($n = 1$).

Correlation PGI-I and Change in Outcome Measures

As can be seen in table 1, the post-treatment change in IIQ-7 and ICIQ-UI-SF correlated significantly with PGI-I.

A subgroup analysis was performed to evaluate if patients with vaginal dryness (reported in the MBS questionnaire), being one of the most frequently reported symptoms associated with VA [18], would respond differently on the PGI-I scale. This analysis revealed that women with and without vaginal dryness reported a similar improvement after topical oestrogen treatment.

Discussion

In this pilot study, we reported both subjective and objective outcome data for women with postmenopausal stress incontinence after vaginal oestriol therapy.

Regarding the primary subjective outcome of this study (PGI-I response), half of the participants reported an improvement after treatment. The response on the PGI-I scale did not differ significantly between patients with or without vaginal dryness as MBS, one of the most frequently reported symptoms associated with VA.

The secondary subjective outcome assessment showed a significant improvement on the UDI stress domain. In accordance with our findings, previous studies have shown a subjective improvement of incontinence after local oestrogen treatment [8, 27].

Of all women who reported PGI improvement after using the cream for 6 weeks, a significant improvement was noted in their answers to the IIQ and ICIQ questions. However, women who reported improvement on the PGI question did not have a significant change in pH, cough pad test or UDI outcomes. This illustrates the fact that there might be relief in terms of alleviating symptoms without an actual objective improvement.

Regarding objective outcome, the change in vaginal pH demonstrated possible objective evidence of treatment benefit, as a decrease in vaginal pH is associated with less VA [18]. It also demonstrates that participants used the prescribed cream, which supports the high self-reported compliance.

Unfortunately, we could not objectify the improvement reported in our study with the cough pad test. A well-validated and commonly used method for quantification of urine loss in clinical studies has traditionally been the 24-hour pad test [21]. This test can however be cumbersome, and a more practical and reliable alternative has been described in the form of the erect cough pad test [26]. In our study however, the erect cough pad test proved to be an outcome measure with a wide variation in measurement both at baseline and after 6 weeks of treatment, probably because of the co-existing urge-incontinence in most participants.

Regarding the design of our study, the duration of treatment of 6 weeks was determined from the recent Cochrane review as likely to demonstrate an effect [7]. It was also chosen on a pragmatic basis, as the waiting time for physiotherapy in 2 of the centres was approximately 6 weeks. After 6 weeks of treatment we observed an improvement in half of the participants, a significant improvement on the UDI stress domain and a significant decrease in vaginal pH. Most studies evaluating the effect of local oestrogens on vaginal pH in patients with VA assessed vaginal pH after at least 12 weeks of treatment. This is in accordance with the FDA recommendations in which follow-up duration of at least 12 weeks is advised for studies evaluating the efficacy of oestrogen treatment for treatment of VA [28]. It could be that for further improvement and reliable assessment of subjective outcome in studies regarding local oestrogen treatment for SUI, follow-up duration of 12 weeks is advisable as well. Waiting times for additional treatment in 2 of the centres was

around 6 weeks. A longer duration of treatment of SUI with just the oestrogen cream in the absence of financial incentive was not ethically justifiable.

Potential limitations of our study need to be addressed. It turned out to be difficult to recruit postmenopausal women with pure SUI, often a concomitant urinary urgency or UUI was present. The criterion for the cough pad test to at least achieve a bladder volume above 200 ml before performing the test was therefore probably too strict. It also shows that pure SUI in postmenopausal women is not very common. Epidemiological reviews reveal that stress incontinence prevalence tends to peak at age 45–49 and fall off thereafter [29]. The peri-menopausal period is associated with an increased risk of UI for all types of UI together and analysis by type of UI shows that this association with the peri-menopause mainly concerns UUI [30].

There are limitations to the way compliance was measured in this study. Medication non-adherence is often defined as taking <80% of prescribed doses, and non-adherence can also include taking too many doses [31]. In this study, the adherence rate seemed higher; however, we used patient self-report measures, which are known to overestimate adherence [31]. We provided an instruction on how to use the cream and in which amount, and although it was difficult to control the amount actually used, the decrease in vaginal pH supports our high medication adherence rate. We feel that the way we provided instructions and assessed compliance was the most feasible option available for all participating centres and represents common clinical practice.

In conclusion, our data show that local oestrogen therapy can reduce SUI symptoms in postmenopausal women; however, the response in the individual is difficult to predict. The pathophysiology of topical oestrogens in the presence of SUI plus VA is not clarified with this study. Topical oestrogen treatment is however a safe and relatively cheap treatment that generates positive results regarding UI that is comparable to other conservative treatments. We recommend that these positive results be further explored in a subsequent study with longer follow-up duration in postmenopausal women with pure SUI without concomitant UUI. It is preferable to incorporate this in a randomised placebo controlled trial design to also investigate a possible placebo effect. Such an RCT will require special recruitment efforts with appropriate funding but is of great value, as topical oestrogen therapy in the treatment of SUI has the potential to achieve a prominent place in the available conservative treatment options.

Acknowledgements

None.

Funding

In South Africa, this study was funded by the South African Menopause Society (SAMS). The Groote Schuur hospital is a public institution with patients having limited financial resources;

therefore, this study would not have been possible if the creams would not have been available to the patients for free. The SAMS provided funding to purchase the cream. No external funding was sought in St. George Hospital Australia and the Academic Medical Centre Amsterdam.

Disclosure Statement

The authors declare that they have no conflict of interest.

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