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A RANDOMISED PROSPECTIVE SINGLE-BLINDED STUDY COMPARING "INSIDE-OUT" VERSUS "OUTSIDE-IN" TRANSOBTURATOR TAPES IN THE MANAGEMENT OF FEMALE STRESS URINARY INCONTINENCE (E-TOT STUDY); 3 YEARS FOLLOW-UP.

Hypothesis / aims of study
To provide a 3-year evaluation of transobturator tension-free vaginal tapes (TO-TVT) in the management of female stress urinary incontinence (SUI) comparing the two surgical transobturator approaches: Inside-out (TVT-O) versus Outside-in (TOT).

Study design, materials and methods
A single-blinded prospective randomised study conducted in a tertiary urogynaecology centre and approved by the research ethics committee. All women admitted for TO-TVT as a sole procedure, in the period between April 2005 and April 2007, were invited to participate; 341 women were recruited and randomised to either inside-out (TVT-O n=170) or outside-in (TOT n=171). Women were included if they had urodynamic SUI or Mixed incontinence with predominantly bothersome SUI, having failed or declined pelvic floor muscle training. Women with pelvic organ prolapse (≥ stage 2 POP-Q) and/ or concomitant surgery were excluded. All women completed symptom severity and quality of life (QoL) questionnaires; Kings Health Questionnaire (KHQ), Pelvic Organ Prolapse/Incontinence Sexual Function Questionnaire (PISQ-12) and Birmingham Bowel Urinary Symptom Questionnaire (BBUSQ-22) pre-and postoperatively at 1 & 3 years. Furthermore, they completed Patient Global Impression of Improvement (PGI-I) and International Consultation of Improvement Questionnaire (ICIQ-SF) at the 1 & 3 years follow-up. The primary outcome at 3-years was "patient-reported success rate" defined as "Very Much Improved" or "Much Improved" on the PGI-I questionnaire. Secondary outcomes included: improvement in women's QoL (≥ 10 points improvement on the total KHQ score) and sexual function (improvement in PISQ-12 scores) and risk factors for late failure of TO-TVT.
Initial power calculation showed that 140 women are required in each arm to detect 10% difference between the 2 procedures with 80% power and assuming 85% success rate for inside-out TVT-O. Between-group comparison was undertaken using Chi-squared tests, Fishers exact test or Mann-Whitney test as appropriate. Within-group comparisons of quantitative variables were done using the Wilcoxon test. McNemar test was used to compare the success rates at 1 year follow-up with success rates at 3 year follow-up. Risk factors for late failure were assessed using univariate and multivariate logistic regression models. All statistical analysis was undertaken using SPSS version 18.0(SPSS, Chicago, IL, USA).

Results
238 women (70%) completed the 3 year follow-up (inside-out n=126 vs. outside-in n=112); including 22 women who underwent further continence surgery and are included in this study as surgical failures (11/22 women had further surgery within the first year). The patient-reported success rate at 3-years was 73% (n=174) with no significant difference between the inside-out and outside-in TO-TVT (72.3% vs. 73.8%; OR 0.927; 95%CI 0.552-1.645; p=0.796). KHQ scores showed ≥10 points improvement in 80.3% (n=191) of the women and there was no significant difference across the two groups; inside-out 84.1% vs. outside–in 75.9%; (OR 1.68; 95%CI 0.88-3.21; p=0.113) Table 1 shows analysis of KHQ domains, and total KHQ scores comparing both procedures. A total of 110 (46.2%) of the women completed a valid PISQ-12 postoperatively and 73.6% (n=81) had an improvement in total PISQ-12 scores while 21% (n=23) had a deterioration in total PISQ-12 scores with no significant difference between both groups [Table1]. There was a significant reduction in patient-reported success rate when comparing 1 vs. 3 years results (80% vs. 73.1%; p=0.005); Univariate analysis showed pre-operative urgency (p=0.017), urgency incontinence (p=0.007) & nocturia (p=0.014) to be potential risk factors for late failure i.e. after initial success at 1-year. However pre-operative "urgency" was shown to be the only independent risk factor for late failure in the multivariate regression model (OR, 3.351; 95%CI, 1.099-10.212; P=0.033)

Interpretation of results
The E-TOT study (1) was the first high quality RCT of the two TO-TVT procedures; the study protocol was registered in the public domain (www.clinicaltrials.gov) in March 2005. At 12 month follow-up, the trial showed no statistically significant difference in patient-reported success rate. A clinically significant improvement in QoL (KHQ scores) was observed favouring inside-out TVT-O. There were no significant differences in peri-operative morbidity and postoperative sexual function in sexually active women. The E-TOT study and a number of systematic/ Cochrane reviews recommended long-term follow-up for adequately powered RCTs if we were to ascertain, not just wonder, how our surgery holds up over time.
The results of this study show patient-reported success rate for TO-TVT at 3 years as 73% with no significant difference between the 2 transobturator routes. The vast majority of responding women continued to show clinically significant improvement in their QoL (80%) & sexual function (73%) at 3 years again with no difference between both routes. The results of this study are unique as there no other similar reported RCTs. Our results are comparable with the 72.9% success rate reported for inside-out TVT-O at 5 years in a recent RCT comparing it to retropubic TVT(2). Unlike the risk factors for early failure at 1-year, only "Urgency" was found to be an independent risk factor for late failure of TO-TVT.

Concluding message
Transobturator tension free vaginal tapes are associated with 73% success rate at 3-years follow up with no significant difference between the two surgical approaches of inside-out and outside-in. Success rates were however significantly reduced when compared to the results of the 1 year follow up with pre-operative "urgency" being the only independent risk factor for late failure.

Table 1: Analysis of KHQ and the PISQ-12 Pre-operatively and at 3-years Post operative.

KHQ Domains	MEDIAN (IQR)		P-VALUE	MEDIAN DIFFERENCE [Pre – @3yrs Post(IQR)		P-VALUE
	PRE-OP	3yr POST OP		Inside-out (TVT-O)	Outside-in (TOT)	
General Health	25(0-25)	25(0-25)	0.882	0(0,12.5)	0 (-25,25)	0.861
Incontinence Impact	100(66.67-100)	0(0-33.3)	<0.001	66.67(33.33,100)	66.67(33.33,100)	0.537
Role Limitation	66.67(33.33-83.33)	0(0-16.67)	<0.001	50(33.33,83.33)	50(33.33,70.83)	0.721
Physical Limitation	66.67(50-83.33)	0(0-16.67)	<0.001	50(33.33,83.33)	50(29.16,83.33)	0.369
Social Limitation	33.33(11.11-66.67)	0(0-0)	<0.001	33.33(11.11,61.11)	22.22(11.11,44.44)	0.242
Personal Relationships	33.33(0-66.67)	0(0-0)	<0.001	33.33(0,58.33)	33.33(0,62.5)	0.653
Emotions	61.11(33.33-88.89)	0(0-22.22)	<0.001	55.56(22.22,77.78)	33.33(22.22,66.7)	0.088
Sleep/Energy	41.67(33.33-66.67)	16.67(0-33.33)	<0.001	33.33(0,50)	33.33(0,50)	0.447
Severity Measure	75(58.33-91.67)	16.67(0-50)	<0.001	50(25,75)	50(16.67,66.67)	0.731
Total KHQ	55.40(41.43-70.31)	9.26 (3.7-24.9)	<0.001	39.81(27.6,59.88)	39.19(21.92,55.24)	0.356
Total PISQ	33(26-36.5)	38(32.75-41)	<0.001	5(0,10)	4(0,6.59)	0.317

References

1. Randomised Prospective Single- Blinded Study Comparing “Inside-Out” Vs “Outside –In” Transobturator Tapes in Management of Urodynamic Stress Incontinence; One year outcomes from the E-TOT study. BJOG 2010; 117:870-8
2. Tension-Free Vaginal Tape Versus Transobturator Suburethral Tape: Five-Year Follow-up Results of a Prospective Randomised Trial. Euro Urol 2010; 58: 671– 677

Specify source of funding or grant	**Henry Smith Charity** **Coloplast**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**www.clinical trials.gov**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**South Glasgow Research Ethics Committee**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**