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The Efficacy of Sham Tension-Free Vaginal Tape® Incisions in Randomized Participants Undergoing Vaginal Prolapse Surgery

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Abstract

Objective—This planned secondary analysis of the Outcomes Following Vaginal Prolapse Repairs and Midurethral Sling (OPUS) trial assessed whether treatment knowledge differed between randomized groups at 12 months and whether treatment success was affected by treatment perception.

Study Design—Sham suprapubic TVT incisions were made in masked OPUS participants randomized to no-TVT. Primary surgical outcomes and maintenance of blinding was assessed at 12 months. Knowledge of treatment assignment was compared between groups, and the relationship with treatment success rates assessed.

Results—Prior to the 12-month post-operative visit, only 4% (13/336) of treated participants formally reported unmasking. At 12 months, 94% (315/336) randomized participants provided treatment knowledge data. Sixteen (10%) TVT participants reported treatment knowledge; most

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(15, 94%) were correct; 17 (11%) of sham participants reported treatment knowledge; half (8, 47%) were correct ($p=0.004$). Similar proportions of unmasked participants who reported no treatment knowledge correctly guessed/perceived treatment assignment [sham 46 (33%) vs TVT 44 (33%)]. We did not detect significant differences in treatment success rates based on perception within and across received treatment groups [perceived sham vs. TVT overall ($p=0.76$)]. Of those receiving TVT, more participants perceiving TVT had treatment success compared to those that perceived sham (84% versus 74%; $p=0.29$). Among sham participants, more participants perceiving sham had success compared to those that perceived receiving TVT (65% vs. 56%; 0.42).

Conclusion—Sham surgical incisions effectively mask TVT randomization. These findings may help to inform future surgical trial designs.

Keywords

Sham incision; Surgical Trial; Stress Urinary Incontinence; Pelvic Organ Prolapse

Introduction

Two critical principles for the proper conduct of a masked randomized trial include successful randomization and maintenance of the randomization assignment masking, also called blinding. Placebo controls have been introduced into clinical study design to enhance these basic tenets of scientifically sound human-subject research and to minimize participant and evaluator knowledge of treatment. Placebo controls have traditionally been useful in situations where there is a potential for significant ‘placebo effect’, as in the case of studies utilizing outcomes based on subjective measures and those involving patient perception. Surgical sham incisions are designed to allow conduct of a study so that treatment arms are indistinguishable to both participant and evaluator and should be low risk.

While many placebo-controlled trials in the study of pelvic floor disorders have focused on pharmacologic or behavioral therapy, there are fewer placebo-controlled trials in the surgical literature. For example, Jarrell et al compared sham surgery (with sham skin incisions) to excision of endometriosis in a randomized controlled trial assessing pain¹. They reported that active surgery (excision) was not associated with improvement in pain over sham incision, as measured by time to repeat surgery.

The Outcomes Following Vaginal Prolapse Repairs and Midurethral Sling (OPUS) trial provided an ideal environment to study the efficacy of sham incisions. In OPUS, women undergoing vaginal prolapse repair were randomized to Tension-Free Vaginal Tape® (commonly known as TVT) versus no TVT with sham suprapubic incisions to mask TVT assignment. We hypothesized that if sham incisions were effective and masking was maintained throughout the course of a trial, then the participants’ perception of treatment would not differ between study groups.

The objective of this planned secondary analysis of the OPUS trial was to determine whether the participant’s knowledge of treatment arm differed between randomized groups

at 12 months and to assess whether treatment success was affected by the perception of receiving active treatment (TVT).

Materials and Methods

This is a planned secondary analysis of the Outcomes Following Vaginal Prolapse Repair and Mid Urethral Sling (OPUS) trial. The design and primary outcome of this trial have been reported^{2, 3}. Briefly, treatment success was defined at 3 months by positive cough stress test and/or bothersome urinary incontinence (UI) or need for UI treatment. All participating sites of the Pelvic Floor Disorders Network had IRB approval and written informed consent was obtained on all patients. Briefly, participants were women considering apical and/or anterior vaginal wall vaginal prolapse repair for stage 2 or greater prolapse without subjective complaints of stress urinary incontinence (SUI). At the time of their vaginal prolapse repair they were randomized to a concomitant tension free vaginal tape (TVT) or sham incisions. At the time of vaginal prolapse surgery in the randomized participants, participants randomized to the control group underwent partial thickness suprapubic skin incisions with the use of a scalpel, located and sized to be identical to the 2 centimeter suprapubic TVT trocar exit incisions performed in women randomized to and receiving the TVT. All incisions, sham and real, were covered by a Steristrip® for one week unless there was a clinical reason for removal (ie. suspicion of a postoperative incision-related bleeding or infection).

A systematic sample of women declining participation in the randomized trial but otherwise eligible for the study was offered participation in a patient preference cohort. Participants in the patient preference cohort chose whether or not to undergo a TVT at the time of their vaginal prolapse surgery and those not receiving a TVT did not have sham incisions placed.

In the randomized cohorts, this analysis addressed whether treatment knowledge differed between randomized groups at 12 months and whether treatment success was affected by the perception of receiving active treatment (TVT). In the patient preference cohort, only assessment of knowledge of treatment and treatment received was assessed. Participants or evaluators could complete a report detailing any unmasking circumstances at any point after study surgery and prior to the 12-month primary outcome surgical assessment. At the time of the surgical outcome assessment at 12 months, treatment knowledge in both randomized and patient preference cohorts was also assessed by the participant by her responding to the query: "Have you found out or been told (by clinical personnel) whether you had the additional study procedure (TVT) at the time of your prolapse surgery? (Yes, No)". Participants who reported "Yes" to this question were considered "unmasked". Additionally participants were asked: "Did you have (Do you think you had) the additional procedure? (Yes, No, Don't Know)". This data was recorded as "perceived" treatment. Treatment perception was compared between treatment groups, and the relationship with treatment success rates was assessed.

All analyses are presented based on received treatment and participants that did not complete the treatment knowledge form are excluded from further analyses. Since all analyses are considered secondary, they are exploratory in nature and resulting p-values are

considered descriptive measures of relationship as opposed to formal tests of hypotheses and therefore no adjustments for multiple comparisons were made. The percent of participants reporting knowledge of treatment received and those correctly identifying treatment assignment among those reporting knowledge as well as those reporting no knowledge was compared by treatment groups using a two-sided chi-square test statistic. These analyses were completed for participants with primary outcome data. We separately analyzed the randomized and patient preference cohorts, with and without participants reporting an unmasking incidence. The relationship of treatment received and perception with treatment success was assessed via a logistic model with the outcome of treatment success and explanatory variables of treatment received, treatment perceived and their interaction. Various comparisons of treatment success were assessed based on two-sided Wald chi-square tests resulting from this model including perceived sham vs. sling (overall and by received treatment group), incorrectly perceiving sling vs. incorrectly perceiving sham, treatment effect (by perception group) and incorrect perception of sling vs. receiving sling. This model included only randomized participants with no treatment knowledge and no unmasking event reported.

Results

In this secondary analysis of 336 randomized and treated participants, 13 (4%) participants had unmasking forms completed during the 12 months after randomization and 315 (94%) completed treatment knowledge forms at 12 months (Figure 1). In the randomized and treated cohort, only 16 in the sling (TVT) and 17 in the sham group (total =33) reported knowing their treatment group at 12 months. The participant reported knowledge of treatment compared to the actual treatment received, excluding and then including participants who completed the unmasking form is shown in Table 1. Approximately 90 % of participants who were not unmasked [140/153 (92%)] in the sham and 135/149 (91%) in the sling groups] stated that they did not know their treatment assignment. Treatment group differences were not significant. ($p = 0.78$ and 0.90 , respectively)

Table 2 summarizes participant-reported treatment perceptions versus treatment received. The vast majority (275/302) of participants without an unmasking incident reported no knowledge of their treatment group. One of these participants did not provide a response to the perception question. For the remaining, 121/274 (44%) of them reported no perception of their treatment, 77/274 (23%) perceived the incorrect treatment, and 76/274 (33%) perceived the correct treatment ($p=0.93$ for comparing correctly perceiving treatment vs. not between treatment groups). For participants reporting knowledge including those with a documented unmasking incidence, their perception was more likely to be correct if they perceived they received a sling 15/16 (94%) than if they received a sham 8/17 (47%) ($p=0.004$). Results were similar excluding or including participants who reported unmasking.

Table 3 summarizes treatment success rates by perceived treatment and treatment received in all randomized, treated participants who remained masked (excluding unmasked participants). There appears to be no evidence of difference in success rates between those who perceived sham 53/77 (69%) versus those who perceived sling 55/76 (72%) ($p=0.76$

overall). In the sling group, those that perceived sling had the highest treatment success rate 37/44 (84%), but this did not significantly differ than those who perceived sham 23/31 (74%, $p=0.29$). Treatment success was no higher in the perceived sham group than in the perceived sling group.

The actual treatment effect was more powerful than the perception effect. Participants who perceived they had a sling and received a sling had a higher treatment success rate 37/44 (84%) than those who perceived they had a sling but actually received sham 18/32 (56%) ($p=0.007$). The actual treatment effect of sling, regardless of participants' perceptions, was greater than the perception effect for participants who perceived sling but actually received sham (102/135, 76% vs 18/32, 56%, $p=0.03$).

The patient preference cohort had 129 participants and 116 (90%) completed the treatment knowledge form (Figure 1). Despite the fact that these participants should know their treatment assignment because they declined randomization and chose whether to receive a sling or not, the majority of patients in the cohort (64 % in the no TVT group and 56% in the sling group, $p=0.37$), reported that they did not know whether they received the sling (Table 4). Of those that reported they knew their treatment, 81% in the no TVT group and 92% in the sling group were correct ($p = 0.27$).

Comment

Placebo controlled randomized surgical trials using a sham incision are rare. To our knowledge, this is the first time that a sham supra-pubic incision for TVT procedure has been used and demonstrated to be an effective masking strategy in a randomized surgical trial. Our finding that only a small number of treated participants in either the TVT (13%) or sham (11%) groups were un-masked by 12 months (had an unmasking incidence reported or reported treatment knowledge) advances our knowledge regarding sham incisions in surgical trials. The effective use of sham is further demonstrated by the lack of difference in the percent of randomized participants who correctly guessed/perceived treatment assignment between groups (33% vs 33%). Our study also confirms the feasibility of sham incisions in randomized surgical trials. There is popular perception that patients and oversight institutional review boards may have a negative reaction and would not accept a placebo arm in surgical trials. However, the majority of participants were willing to accept randomization to a group with a sham incision, even when given an option for the patient preference cohort.

Other studies that have used a sham have suggested a significant placebo response accounting for up to 35% of the response⁴. Interestingly, we did not find a significant placebo effect, there appears to be no evidence of difference in success rates between those that perceived receipt of sham vs. sling. In addition, the actual treatment effect of sling (regardless of each participant's perception) was greater than the perception effect for participants that perceived sling but actually received sham (76% vs. 56%, $p=0.03$). The lack of a placebo response may be important in designing and interpreting future TVT surgical trials and should not be interpreted to mean that masking maintenance is not important. The maintenance of masking in a placebo-controlled trial can significantly impact subjective

assessments of treatment success. This may explain the smaller difference of treatment effect in the primary outcome of the study compared to another randomized trial using TVT to prevent incontinence ^{3, 5}.

An unexpected finding was the lack of group assignment recall amongst participants who selected their group assignment in the patient preference participants. Despite lack of masking, only 40 % of 116 women who completed the treatment knowledge form reported knowing their assignment. This demonstrates a low patient recall of the sling procedure since participants in this group were aware of their assignment during the operative decision making and counseling. As there was no site difference, variation in patient counseling is unlikely to be a factor. As we did not ask the participants to recall other aspects of their surgery, we are limited in our interpretation of this finding and we do not know if participants had difficulty recalling other aspects of their care or just their anti-incontinence procedure. Women may have perceived prolapse repair as the main portion of the surgery and the TVT as secondary since it was performed as a preventative measure. It may also represent a challenge in the complicated consent process for pelvic reconstructive surgery. This is supported by recent studies showing deterioration of patient understanding of surgical counseling hours ⁶ or weeks after gynecologic and mid-urethral sling surgery ⁷.

Although the use of sham incisions was effective in this trial, future trials considering this design will need to address ethical and design challenges. For instance, if there is acknowledged debate regarding the best treatment for an illness and if that debate centers on no treatment versus surgical treatment, then a sham surgery could be ethically justified ⁸. However, even when uncertainty exists regarding the benefit of accepted surgical interventions, it can be difficult to establish equipoise in surgical trials due to patient or surgeon perceptions of benefit ⁹. Placebo controlled randomized surgical trials limit confounding and biases when studying benefits and harms. Our results can be used to encourage other surgical trialists to consider the use of placebo-controlled designs with sham incisions when planning randomized surgical trials.

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Appendix

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Figure 1.

Algorithm of study randomization, participant reported unmasking, and treatment knowledge form completion.

Table 1

Participant Reported Knowledge of Treatment vs. Treatment Received in the Randomized Cohort

Data Analysis Group	Participant Reported Knowledge	Received Sham n=173	Received Sling (TVT) n=163	p-value ^[1]
Excluding Participants Reporting Unmasking (n=302)	Reported not knowing treatment	140 (92%)	135 (91%)	0.78
	Reported knew treatment	13(8%)	14(9%)	
Including Participants Reporting Unmasking (n=315)	Reported not knowing treatment	142 (89%)	140 (90%)	0.90
	Reported knew treatment	17 (11%)	16 (10%)	

^[1] p-value based on a two-sided chi-square test-statistic of the 2×2 frequency table.

Table 2

Participant-Perceived Treatment vs. Treatment Received in the Randomized Cohort

Data Analysis Group	Participant reported Perception of Treatment	Received Sham n=173	Received Sling (TVT) n=163	p-value ^[1]
Participants Reporting No Knowledge of Treatment and Excluding Participants Reporting Unmasking (n=274)	Don't know	61 (44%)	60 (44%)	0.93
	Perceived sham	46 (33%)	31 (23%)	
	Perceived sling	32 (23%)	44 (33%)	
Participants Reporting Knowledge of Treatment and Excluding Participants Reporting Unmasking (n= 27)	Don't know	1 (8%)	0 (0%)	0.003
	Perceived sham	5 (38%)	1 (7%)	
	Perceived sling	7 (54%)	13 (93%)	
Participants Reporting Knowledge of Treatment and Including Participants Reporting Unmasking. (n= 33)	Don't know	1 (6%)	0 (0%)	0.004
	Perceived sham	8 (47%)	1 (6%)	
	Perceived sling	8 (47%)	15 (94%)	

^[1] p-value based on a two-sided chi-square test-statistic of a 2×2 frequency table of whether participant-reported treatment correctly matched received treatment vs. treatment received where responses of “Don't know” were considered incorrect treatment assignment.

Table 3

Treatment Success Rates by Treatment Perceived and Treatment Received for Randomized Participants*

Treatment Perceived	Received Sham n=173	Received Sling (TVT) n=163
Don't know	35/61 (57%) A.	42/60 (70%) B.
Perceived sham	30/46 (65%) C.	23/31 (74%) D.
Perceived sling	18/32 (56%) E.	37/44 (84%) F.
P-values for Comparisons of Interest ^[1]		
Perception effect overall: perceived sham vs. perceived sling: C+D vs. E+F		0.76
Perception effect among those that received sling: D vs. F		0.29
Perception effect among those that received sham: C vs. E		0.42
Perceived sling (but received sham) vs. perceived sham (but received sling): E vs. D		0.13
Treatment effect among perceived sling: E vs. F		0.007
Treatment effect among perceived sham: C vs. D		0.40
Perceived sling (but received sham) vs. received sling (including Don't know): E vs. B+D+F		0.03

^[1] p-values based on a two-sided Wald chi-square test-statistic from a logistic model

* Excluding Participants Reporting Unmasking and Those Reporting Having Treatment Knowledge

Table 4

Patient-Preference Cohort Participant Knowledge of Treatment and Treatment Received

Participant Reported Knowledge (n=116)	Received no TVT (n=59)	Received TVT (n=57)	p-value
Reported not knowing treatment (n=70)	38 (64%)	32 (56%)	0.37 [1]
Reported knew treatment (n=46)	21 (36%)	25 (44%)	
Among Those Reporting Knowledge of Treatment (n=46)			
Don't know	1 (5%)	1 (4%)	0.27 [2]
Reported received no TVT	17 (81%)	1 (4%)	
Reported received TVT	3 (14%)	23 (92%)	
Among Those Reporting No Knowledge of Treatment (n=32)			
Don't know	13 (34%)	13 (41%)	0.86 [2]
Reported received no TVT	18 (47%)	10 (31%)	
Reported received TVT	7 (18%)	9 (28%)	

[1] p-value based on a two-sided chi-square test-statistic of the 2×2 frequency table.

[2] p-value based on a two-sided CMH test-statistic of a 2×2 frequency table of whether participant-reported treatment correctly matched received treatment vs. treatment received where responses of “Don't know” were considered incorrect treatment assignment.