29

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STRESS INCONTINENCE AFTER RADICAL PROSTATECTOMY: A RANDOMIZED CONTROLLED TRIAL ON COMBINATION OF DULOXETINE AND REHABILITATION VERSUS REHABILITATION ALONE

Hypothesis / aims of study
At the present time there is no pharmacological treatment approved for stress urinary incontinence (SUI) in male. Pelvic floor muscle training (PFMT) decreases the frequency of incontinence episodes and reduces leakage compressing urethra during activity. While duloxetine (DLX) it is supposed to increase rhabdosphincter tone and contraction stimulating the pudendal nerve. Pelvic floor muscle and rhabdosphincter are not supply by the same nerves and pelvic floor exercises do not activates urethral sphincter, so these preliminary considerations indicate that PFMT and DLX could have cumulative effects on male post-RRP SUI. Furthermore, unlike women with SUI, the majority of male patients recover urinary control 1 year after radical prostatectomy, due to the natural recover of sphincter function, so everything point to the fact that DLX in male incontinence could employed only for a limited time. The aims of this study is to assess DLX efficacy and safe in men with SUI after radical retropubic prostatectomy (RRP), to evaluate the effect of association of DLX and PFMT, to compare combined treatment versus PFMT alone, to assess long term effect of combined treatment even after DLX planned discontinuation.

Study design, materials and methods
This prospective, randomized, double blind, placebo controlled study was conducted between January 2005 and March 2006; 153 patients undergone standard RRP were considered for this protocol, 10 days after catheter removal 112/153 RRP patients were randomized to receive PFMT and 40 mg DLX twice daily (group A), or PFMT and placebo (Group B), for 16 weeks. The case definition included predominant symptoms of post-RRP SUI with an average of at least 4 stress incontinent episodes daily, the absence of symptoms of urge incontinence, a positive 1 hour pad test. The exclusion criteria were the presence of pre-operatively incontinence and/or history of OAB symptoms. After 16 weeks of treatment both groups discontinued placebo or DLX and continued PFMT only. All patients was invited to complete Incontinence quality of life (I-QoL) questionnaire and bladder diary during last week before randomization and before each control visit. Patients were informed about the off-label use of duloxetine, about possible side effect and then they signed an informed consent form which had been previously approved by the Ethics Committee of our Institution. Follow-up included controls at 4, 10, 16, 20 and 24 weeks after randomization. The efficacy of treatment was evaluated objectively using 3 variables: the 1 hour pad test, the I-QoL questionnaire, the incontinence episode frequency (IEF). A responder was defined as a subject with a reduction of IEF of 50% or more. Incontinence was measured by the number of pads used daily, we defined continence the use of 0 pad. Safety of treatment was assessed by documenting treatment emergent adverse events (AE), the number of discontinuation due to AE, vital signs and laboratory measurements. *Statistical analysis*: unpaired two-tailed t test to compare, age and pre-treatment pads use between two groups, and paired t test to compare pre and post-treatment pads use for the 2 groups at 4, 10, 16, 20 and 24 weeks; Fischer's exact test to compare differences in the proportion of patients in the 2 groups who were continent at 4, 10, 16, 20 and 24 weeks.

Results
A total of 112 men were randomized to treatment with PFMT and DLX or placebo, 10 (11,2%) of these patients discontinued study prematurely for AE, 1 (1,8%) for placebo and 9 (15,2%) for DLX (P=0,01), with nausea the most common reason for discontinuation (70%). Overall 102 men completed the 24 weeks study, 50 in group A, 52 in group B. Significant improvements were demonstrated in both groups even from first weeks of treatment (p<0,0001). After 4 weeks 16 patients were completely dry in group A and 6 in group B (P=0,01). After 10 weeks 30 patients in group A and 14 in group B (P=0,001). After 16 weeks completely continence was achieved by 39 patients in group A as opposed to 27 in group B (p=0,007). At 20 weeks, 4 weeks after planned discontinuation of DLX and placebo, we observed an U-turn, 23 patients were completely dry in group A while 38 were in group B (p=0,008). Whereas after 24 weeks 31 in group A versus 41 in group B (P=0,08). Combined treatment group showed significant improvements in I-QoL scores compared whit PFMT only group, these results were apparent by the first control visit but they do not maintained throughout the study.

Interpretation of results
We observed a positive impact on achieving early continence in patients treated with combination of rehabilitation and DLX, results were statistical significant for the first 4 months during the assumption of drug; but during the other 2 months we observed an inversion of these results. We thought that DLX and rehabilitation had additional effect with a significantly reduction of incontinence episodes respect PFMT alone, this is real until drug's assumption; but at planned duloxetine's discontinuation PFMT only group had better continence, like as patients treated with DLX didn't learn to reproduce the contraction during effort as well as PFMT only patients.

Concluding message
DLX and PFMT had additional effect with a significantly reduction of incontinence episodes respect PFMT alone in post-RRP incontinence, the data suggest that combination therapy might provide another treatment option for SUI in men that might postpone surgery solution.

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CLINICAL TRIAL REGISTRATION: **This clinical trial has not yet been registered in a public clinical trials registry.**

HUMAN SUBJECTS: **This study was approved by the Ethics Committee: Dipartimento Medico-Chirurgico, Azienda Ospedaliero-Universitaria Careggi, Firenze and followed the Declaration of Helsinki Informed consent was obtained from the patients.**