Spinal Cord Injury Induced Arrest in Estrous Cycle of Rats Is Ameliorated by S-nitrosoglutathione: Novel Therapeutic Agent to Treat Amenorrhea

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Abstract

Introduction. Amenorrhea following spinal cord injury (SCI) has been well documented. There has been little research on the underlying molecular mechanisms and therapeutics.

Aim. The purpose of the present study was to investigate the effect of GSNO in ameliorating SCI-induced amenorrhea through affecting the expression of CX43, NFκB, and ERβ protein.

Methods. SCI was induced in female SD rats at the T9-T10 level. Estrous stage was determined by vaginal smear. GSNO (50 mg/kg body weight) was gavage fed daily. Animals were sacrificed on day 7 and 14 post SCI. Ovaries were fixed for histological and biochemical studies. Expression levels of ERβ, CX-43, and NFκB were analyzed by Western blot and immunofluorescence.

Main Outcome Measures. GSNO hastens resumption of the estrous cycle following SCI-induced transient arrest.

Results. Resumption of estrous cycle was hastened by GSNO. Atretic and degenerating follicles seen in the ovary of SCI rats on day 14 post-SCI were decreased in GSNO treated animals. The increased CX43 expression observed with SCI ovary was decreased by GSNO. ERβ expression decreased significantly on day 7 and 14 post-SCI and was restored with GSNO treatment. Following SCI, NFκB expression was increased in the ovarian follicles and the expression was reduced with GSNO administration. The number of terminal deoxynucleotidyl transferase-mediated biotinylated uridine triphosphate (UTP) nick end labeling positive follicular and luteal cells was increased after SCI. GSNO-treated animals had significantly fewer apoptotic cells in the ovary.

Conclusion. SCI-induced amenorrhea is accompanied by an increase in CX43 expression and a decrease in ERβ expression. SCI animals treated with GSNO resumed the estrous cycle significantly earlier. These results indicate a potential therapeutic value for GSNO in treating amenorrhea among SCI patients.

Editorial comment: This paper investigated if exogenous GSNO (S-nitrosoglutathione) administration hastened the transient arrest in estrous cycle induced by spinal cord injury (SCI). Authors verified if GSNO therapeutic effect involved ovary alterations in cell apoptosis, inflammation, estrogen receptor β (ERβ) and connexin 43 (CX-43). Virgin Sprague-Dawley female rats were used and SCI was induced at the T9-T10 level. SCI animals were assigned to two groups: GSNO (0.05 mg/kg, oral gavage) every 24 hours until the end of the experimental period (7 and 14 days post SCI) and vehicle (PBS). Sham animals underwent all the procedures except spinal injury. It was observed a significant difference in the recovery of the estrous cycle between vehicle and GSNO-treated group. Vehicle-administered animals acquired regular estrous cycle after 21±1.41
days, while GSNO group in 12.83±1.35 days. Estrous cycle of sham operated animals was not affected and the animals showed regular 4 day cycle. Consequently, GSNO mediated structural changes in the ovaries of SCI rats at 14 days after injury. Sham animals showed degeneration of corpus luteum leading to the formation of corpus albicans and presented many ovarian follicles in the secondary follicle stage. Vehicle treated ovaries of SCI rats showed defective corpus albicans formation, tissue sparing and atrophying secondary follicles. GSNO-treated SCI ovaries showed no tissue degeneration and the cellular architecture resembled that of sham animals, with normal healthy secondary follicles. Since interruption in signaling due to SCI alter ovarian physiology through apoptosis and inflammation, it was evaluated the effects of GSNO-treatment in reverting these mechanisms. TUNEL assay demonstrated that, when compared with the vehicle group, GSNO was effective in inhibiting SCI-induced cellular apoptosis in the ovary. Translocation to the nucleus of nuclear factor kB (NFkB) was inhibited by GSNO administration, ameliorating the inflammatory response. As paracrine signaling is important to endocrine signaling, it was examined how NFkB-mediated signaling was conveyed among ovarian cells. CX-43, a gap junctional intercellular connection, is involved in ovary follicular maturation and potentially related to SCI-induced ovarian pathology. In fact, CX-43 was found upregulated in vehicle-treated ovaries at both days 7 and 14 post SCI, being this effect reversed by GSNO administration. In addition, ERβ expression levels in the ovaries were also evaluated. A decrease in ERβ was seen in vehicle-treated SCI ovaries (days 7 and 14), which levels were increased by GSNO therapy. This study demonstrated a faster recovery from SCI-induced transient arrest in the estrous cycle of GSNO-treated SCI rats, through the modulation of several mechanisms in the ovary. Overall, it seems that low-dose GSNO supplementation may provide an effective therapeutic approach to restore the normal ovulation process in SCI patients of reproductive age; however this needs to be addressed in the clinical setting.

By: CARLA COSTA
Review: Psychosocial interventions addressing sexual or relationship functioning in men with prostate cancer.
Chisholm KE, McCabe MP, Wootten AC, and Abbott J-AM.


ABSTRACT
Introduction. Although previous research has evaluated the effectiveness of psychosocial interventions for men with prostate cancer, no previous review has investigated the effects of psychosocial interventions on both sexual and relationship functioning. Aim. To review the effectiveness of psychosocial interventions that focus on sexual and/or relationship functioning for men with prostate cancer and their partners.
Method. A systematic literature review of research reported in the Medline, PsychINFO, PsychArticles databases from January 1990 to September 10, 2011. Main Outcome Measure. The review focused on the evaluation of interventions that aimed to improve the sexual and/or relationship functioning of men and their partners.
Results. There was evidence that psychosocial interventions can improve men’s sexual functioning, particularly when delivered face-to-face and when using more complex strategies to target sexuality in men and in relationships. There was inconclusive evidence for the effectiveness of psychosocial interventions in improving men’s relationship functioning or the sexual or relationship functioning of their partners.
Conclusions. There is a need for further research to target improving and measuring men and their partner’s sexual and relationship functioning in the context of prostate cancer. The effectiveness of tailoring interventions to the specific needs of men and to their stage of cancer also needs to be further examined.

Comments: ED is highly prevalent in men treated for prostate cancer, even though erections may return, many men experience ongoing erectile difficulties at up to 4 to 5 years posttreatment. Although there are several medical treatments available to treat ED, there are large variations in reported efficacy rates. Failure of medically based treatments to provide sufficient improvement in erectile and sexual functioning has led to an increased focus and interest in psychosocial interventions. Given the importance of the couple’s relationship in the context of coping with prostate cancer, and the close association between sexual and relationship functioning, a review the literature concerning this subject is welcome. It has focused on interventions that targeted sexual and/or intimate partner relationship functioning, and it was found that there was considerable variability in the attention to these aspects and in the types of psychosocial interventions used. Further research is needed with RCTs including larger sample sizes with different stages of disease, ethnicity, sexual orientation, and relationship status; comprehensive use of sexual and relationship functioning measures; tailored intervention components; and inclusion of preplanned moderator variables. In terms of tailoring, future research could develop and evaluate interventions that screen for erectile problems, bother and concern about erectile problems, and relationship difficulties. Specifically, research could be designed to isolate which kinds of treatment are most effective for varying needs of men and stages of cancer. Finally, RCTs could also be employed to compare the efficacy of more than one intervention, for example, couple sex therapy vs. an educative/supportive intervention.

Efficacy and safety of testosterone in the management of hypoactive sexual desire disorder in postmenopausal women.
Davis SR and Braunstein GD.


ABSTRACT
Introduction. Hypoactive sexual desire disorder (HSDD) is a common problem in postmenopausal women, but in the absence of an approved medical treatment in the United States, off-label testosterone use is widespread. Large, randomized controlled studies have demonstrated that transdermal testosterone improves sexual function and activity in postmenopausal women and has favorable short-term safety. However, a longer-term safety profile of testosterone must be established before a testosterone product for women is approved.
Aim. To review current knowledge of the efficacy and safety of transdermal testosterone based on presentations at a satellite symposium during the 2011 annual meeting of the International Society for the Study of Women’s Sexual Health. Methods. Pertinent information included in the presentations was augmented with relevant articles from the peer-reviewed literature. Main Outcome Measures. The rationale for testosterone therapy and results from phase III and other clinical studies with the testosterone patch in postmenopausal women with HSDD and findings from studies investigating the cardiovascular, breast, and endometrial effects of testosterone therapy. Results. Randomized, double-blind, placebo-
controlled studies have established the efficacy of the transdermal testosterone patch for relieving symptoms of HSDD in surgically and naturally menopausal women with and without concomitant estrogen or estrogen/progestin therapy. The main side effects reported in clinical trials were increased hair growth and acne. Available safety data for testosterone, although not conclusive, were reassuring with respect to cardiovascular, breast, and endometrial outcomes. Interim data from a long-term phase III safety trial of a testosterone gel demonstrate a continued low rate of cardiovascular events and breast cancer in postmenopausal women at increased cardiovascular risk.

Conclusion. Transdermal testosterone appears to be an effective and safe therapy for postmenopausal women with HSDD.

Comments: Much of the long-term safety data on testosterone from observational and retrospective studies is clouded by methodological issues, particularly confounding by concurrent administration of estrogen or estrogen and progestin. The main adverse effects following physiologic doses of testosterone are androgenic side effects, primarily increased hair growth, and, in some but not all studies, acne. Transdermal testosterone therapy in women has not been found to have an adverse cardiovascular profile. Furthermore, low-dose testosterone is safe with regard to the endometrium and breast, and both experimental and short-term clinical studies suggest a breast-protective effect of testosterone. A recent summary of the 4-year open-label extension safety data from 967 surgically menopausal women receiving estrogens provides additional reassurance of the safety of testosterone when administered in physiological concentrations. At least, the current widespread practice of off-label prescribing of testosterone products in women raises serious safety concerns and highlights the need for an approved treatment for women. Ideally, future long-term safety studies will be performed in prospective, randomized testosterone vs. placebo-controlled studies in postmenopausal women while controlling for the subgroups of patients on concomitant estrogens, estrogens plus progestin, or those not receiving adjunctive hormone therapy. Such studies will need to be adequately powered to detect safety issues between those on testosterone or placebo, which can be carried out either with a very large population of women as was done in the Women’s Health Initiative Study or by populating a study with women predisposed to develop a condition of interest, such as the current study designed to examine cardiovascular safety during 5 years of use of a testosterone or placebo gel.

BY BEATRICE CUZIN
Simultaneous Penile Lengthening and Penile Prosthesis Implantation in Patients with Peyronie’s Disease, Refractory Erectile Dysfunction, and Severe Penile Shortening.


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Introduction. Due to loss of length, patients who had penile prosthesis implantation for Peyronie’s disease (PD) show a statistically significant reduction in their levels of satisfaction when compared with the general implant population. Aim. The aim of this study is to report our experience of penile lengthening with circumferential graft during penile prosthesis implantation in patients with PD and severe penile shortening.

Methods. Between March 2006 and February 2008, 23 patients with PD, refractory erectile dysfunction, and severe penile shortening underwent penile lengthening with circumferential graft and concomitant implantation of an inflatable penile prosthesis.

Main Outcome Measures. Surgical outcome and complications have been recorded during postoperative follow-up. Patients’ satisfaction has been assessed 6 months postoperatively with the administration of the modified Erectile Dysfunction Index of Treatment Satisfaction (EDITS) questionnaire.

Results. After an average follow-up of 22 months (range 6–36), 20 patients attended all the postoperative follow-up visits and returned the EDITS questionnaire. An average length gain of 2.8 cm (range 2.2–4.5) was recorded, and all patients were able to cycle the device and engage in penetrative sexual intercourse. Patient recorded complications included diminished glans sensitivity in four (20%) and persistent dorsal curvature of less than 15° in three (15%). Overall, 18 patients (90%) were satisfied with the cosmetic and functional result of surgery.

Conclusion. Penile lengthening with circumferential graft during penile prosthesis implantation in patients with PD represents a safe and reproducible technique that yields higher satisfaction rates than penile prosthesis implantation alone in patients with severe penile shortening.

Editorial comment:
Up to 50% of patients with Peyronie’s Disease (PD) are dissatisfied with their postoperative penile length after penile prosthesis implantation (PPI). This series reports the long-term outcome (between March 2006 and February 2008, 23 patients, 22 month follow-up), from patient’s and surgeon perspective, of simultaneous penile lengthening and penile prostheses implantation in patients with PD, refractory ED, and severe penile shortening.

Surgery includes basically a circumferential incision of the tunica albuginea at the level of maximum curvature, and complete stretching, only limited by the length of the neurovascular bundle. The tunical defect was then covered with an InteXen® (American Medical Systems, Minnetonka, MN, USA) patch graft using a continuous 4-0 polydioxanone suture. The width of the tunical defect was measured on the convex and concave aspect of the shaft, with the penis in full stretch. The average graft size was 3.1 cm in width and 12.4 cm in circumference. The corpora were then dilated through the corporotomies and the cylinders of the inflatable device inserted and inflated to around 80% of maximum capacity.

After an average follow-up of 22 months (6–36), all patients were able to cycle the device correctly and to achieve rigidity adequate for penetrative sexual intercourse. The average length gain was 2.8 cm. Overall, 18 patients (90%) were satisfied with the cosmetic and functional result of surgery.

Although this technique seems to be very aggressive, the present series confirms that penile lengthening with a circumferential graft during penile prostheses implantation is a safe and reliable technique in patients with PD, refractory ED, and severe penile shortening.

This promising approach could be considered as a good option in order to achieve higher patient satisfaction in these cases, when compared with penile prosthesis implantation alone. The authors should be congratulated on such a brave attitude, bearing in mind that modelling and small grafts can solve the average needs of penile straightening. With this technique straightening and lengthening are combined, which is usually closer to the patient expectations. Sometimes, an apparently riskier approach is needed to get the best results.

BY NATALIO CRUZ