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European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 189–196 of this issue

Somatic to Autonomic Nerve Grafting for the Treatment of Erectile Dysfunction: It Seems to Work, But How?

Zach S. Dovey, Ash K. Tewari *

Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Although the introduction of robotic technology has reduced the incidence of erectile dysfunction (ED) after radical prostatectomy (RP), it remains a significant problem adversely affecting patients' quality of life [1]. Some patients have reported that potency is more important to them than cancer survival when considering treatment options [2]. Two recent studies have explored somatic to autonomic nerve grafting in humans as a treatment for refractory ED after RP with encouraging results. Souza Trinedade et al. [3] described a novel penile reinnervation technique using four sural nerve grafts with end-to-side neurorraphies connecting bilaterally the femoral nerve to the corpora cavernosa and the dorsal penile nerves. Ten patients were enrolled, six of whom were subsequently able to achieve full penetration at a mean of 13 mo after reinnervation surgery. In this issue of *European Urology*, Reece et al. [4] describe microsurgical techniques with bilateral end-to-side sural nerve grafts from a selective fascicular neurotomy of the femoral nerve to the corpora cavernosa. They enrolled 17 patients and at 12 mo after nerve grafting, 12 patients had erectile function sufficient for satisfactory sexual intercourse. In both studies, all patients had medically refractory ED, underwent nerve grafting on average more than 2 yr after RP, and, potentially, would otherwise have been offered a penile prosthesis. Both studies describe few complications such as minor wound infections, areas of paraesthesia and anaesthesia, and one neuroma [3,4]. By contrast, penile prosthesis surgery is known to be relatively morbid with problems that include infection, erosion, penile necrosis, and malfunction [5]. Their techniques differed somewhat, as Reece et al. [4] did not describe direct femoral-to-dorsal penile nerve grafting, but rather laid 6 cm of sural nerve within the bodies of the corpora cavernosa on each side. For all their patients, Souza Trinedade et al. [3] performed direct sural nerve grafting onto both the dorsal penile nerve and the corpora cavernosa.

Nerve grafting in the limbs is well established, with reasonable outcomes that depend on patient age, the degree of nerve injury, and timing [6]. The choice of autograft depends on limiting postoperative deficit as well as the size and ease of harvesting, with the sural nerve being the commonest choice (eg, for upper limb nerve grafting) and end to end the commonest technique [6]. End-to-side anastomotic techniques are also described, especially in facial reanimation [7]; however, the use of cavernosal interposition end-to-end nerve grafting to improve erectile function has been less successful. A well-designed randomized controlled trial failed to demonstrate any potency benefit of unilateral end-to-end sural nerve grafting at the time of RP [8]. This finding was supported by a retrospective analysis for 36 patients by Kung et al. [9], who found that bilateral nerve-sparing during robotic RP outperformed both unilateral and bilateral interposition end-to-end sural nerve grafting in terms of postoperative potency rates.

The new technique of somatic to autonomic nerve grafting described shows promising results and we commend Reece et al. [4] for undertaking this interesting study. At present the mode of action is not clear, and given that the femoral nerve is under the control of central motor pathways without links to autonomic pathways controlling erectile function, the positive results are intriguing. Reece

DOI of original article: https://doi.org/10.1016/j.eururo.2019.03.036.
* Corresponding author. Department of Urology, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10075, USA. Tel. +1 212 2418971.
E-mail address: ash.tewari@mountsinai.org (A.K. Tewari).

https://doi.org/10.1016/j.eururo.2019.04.020

et al. [4] suggest that neurotransmitter release into the corpora cavernosa is pivotal in recovering potency, although somatic motor axons release acetyl choline and the neurotransmitter at cavernosal neuromuscular junctions is nitrous oxide, whereas Souza Trinedade et al. [3] propose that there is central neural plasticity. Other mechanisms may include the release of neurotrophic factors with cavernosal muscle rehabilitation, plasticity at the cavernosal neuromuscular junction to release appropriate neurotransmitters, and possibly retrograde stimulation of remnant nerve fibers causing regeneration of axons in the cavernosal nerve. We would suggest collaboration with a neuroscientist who has an interest in autonomic neurophysiology, and further animal studies with detailed immunohistochemical analysis of nervous and cavernosal muscle tissue to assess for neural regeneration and neurotrophic factors may give further insight into the mode of action for this technique. Dong et al. [10] undertook such a study in rats, anastomosing autonomic to somatic spinal roots, and demonstrated new neural pathways via retrograde tracing and neural regeneration via histological analysis. Clarifying a specific mode of action would provide support for the design of a larger human study to assess the benefits of this technique in more detail, which we feel is warranted on the basis of the preliminary results.

We also remain advocates for penile rehabilitation with 5-phosphodiesterase inhibitors and intracavernosal injection therapies to prevent chronic cavernosal muscle damage secondary to hypoxia, and promote all activities that improve nerve-sparing techniques. This includes an intricate understanding of pelvic plexus and “hammock” neuroanatomy, as well as minimization of tissue traction and cautery. There are other potential novel treatments that require further study and are also worthy of mention. For example, neurotrophins and amniotic membranes applied to the cavernosal nerve intraoperatively, RhoA kinase inhibitors for penile rehabilitation, penile extracorporeal shockwave therapy, and stem cell therapy [11]. Stem cell therapy via intracavernosal injection shows particular promise, with potential for point-of-care harvesting of autologous adipose-derived stem cells in a solution known as the *stromal vascular fraction* [12]. This is taken from the patient via liposuction and has shown tissue regeneration capacity in human trials for a number of other conditions such as osteoarthritis, cartilage repair, and autoimmune diseases.

Ultimately, we strongly support all innovations that tackle the ongoing problem of ED after RP, and hope that combining efforts and collaborating across disciplines will improve the treatment of ED regardless of its etiology.

Conflicts of Interest: Dr. Ash Tewari , as of 2019.
Listed by COMPANY, RELATIONSHIP STYLE, FINANCIAL INTEREST
Axogen, Scientific Study or Trial, Yes
Boston Scientific Corporation, Sponsored Research, No
Chris Lange Foundation, Donation, Yes
Craig Effron Foundation, Donation, Yes
DNA Based Bicistronic Vectors with Inducible and Constitutive Promoters - ID#: 160608, Patent, No
Global Prostate Cancer Research Foundation, Leadership Position, No
High Intensity Focus Ultrasound and CPG-Brachyury-siRNA for Treatment of Prostate Cancer - ID# 160403, Patent, No
Intuitive Surgical, Scientific Study or Trial, Yes
Kalyani Prostate Cancer Institute, Leadership Position, No
Medtronic, Inc. (10/15/2013), Sponsored Research, No
NIH RO1 Funding -PI, Funding, Yes
Patent for a Catheterless Device and Approach, Patent, No
Peter Georgescu Foundation Award, Leadership Position, Yes
Peter Kalikow Foundation, Donation, Yes
Postgraduate Institute for Medicine, Teaching/Lectures, No
*Promaxo, Leadership Position, Yes
*Promaxo, Equity Ownership. Yes
Prostate Cancer Foundation, Leadership Position, No
Roivant, Consultant, No
Siemens, Advisory, Yes
Tim O'Neill Foundation, Donation, Yes
Urethral Catheterless Radical Prostatectomy, Patent, No
***PROMAXO: Common Stock Certificate VALUE: 51,205 % SHARE RELATED PARTY: 0.63**
-Intuitive - no salary/ see referenced COI's
-Promaxo - no salary/investment - see referenced COI's
-Kite Pharma: Serve as PI. Industry funded for research procedures. Site PI performance - no salary
-Poly ICLC : Serve as site PI. Phase I Study of IN SITU Autologous Vaccination Against Prostate Cancer With Intratumoral and Systemic HILTONOL (POLY-ICLC) Prior to Radical Prostatectomy. Product provided free of charge - no other funding. No salary
*Dr. Ash Tewari (the Principal Investigator in this study and Chairman of Milton and Carroll Petrie Deparmtent of Urology a the Icahn School of Medicine at Mount Sinai) owns equity in the form of stock certificates in Promaxo, for which he serves as an advisor. Promaxo is a privately traded company which develops MRI technology with a focus on prostate cancer.

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