SEXUAL MEDICINE REVIEWS

Bilateral Cavernous Nerve Crush Injury in the Rat Model: A Comparative Review of Pharmacologic Interventions

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ABSTRACT

Introduction: It is common for men to develop erectile dysfunction after radical prostatectomy. The anatomy of the rat allows the cavernous nerve (CN) to be identified, dissected, and injured in a controlled fashion. Therefore, bilateral CN injury (BCNI) in the rat model is routinely used to study post-prostatectomy erectile dysfunction.

Aim: To compare and contrast the available literature on pharmacologic intervention after BCNI in the rat.

Methods: A literature search was performed on PubMed for *cavernous nerve* and *injury* and *erectile dysfunction* and *rat*. Only articles with BCNI and pharmacologic intervention that could be grouped into categories of immune modulation, growth factor therapy, receptor kinase inhibition, phosphodiesterase type 5 inhibition, and anti-inflammatory and antifibrotic interventions were included.

Main Outcome Measures: To assess outcomes of pharmaceutical intervention on erectile function recovery after BCNI in the rat model. The ratio of maximum intracavernous pressure to mean arterial pressure was the main outcome measure chosen for this analysis.

Results: All interventions improved erectile function recovery after BCNI based on the ratio of maximum intracavernous pressure to mean arterial pressure results. Additional end-point analysis examined the corpus cavernosa and/or the major pelvic ganglion and CN. There was extreme heterogeneity within the literature, making accurate comparisons between crush injury and therapeutic interventions difficult.

Conclusions: BCNI in the rat is the accepted animal model used to study nerve-sparing post-prostatectomy erectile dysfunction. However, an important limitation is extreme variability. Efforts should be made to decrease this variability and increase the translational utility toward clinical trials in humans. **Haney NM, Nguyen HMT, Honda M, et al. Bilateral Cavernous Nerve Crush Injury in the Rat Model: A Comparative Review of Pharmacologic Interventions. Sex Med Rev 2017;X:XXX–XXX.**

Key Words: Cavernous Nerve; Crush Injury; Radical Prostatectomy; Erectile Dysfunction; Rat Model

INTRODUCTION

Erectile dysfunction (ED) is a common sequela of radical prostatectomy for the treatment of prostate cancer, even with nerve-sparing and modified nerve-sparing techniques.[1,2] There are options for men with post-prostatectomy ED, such as alprostadil injections, vacuum erection devices, and phosphodiesterase type 5 inhibitors (PDE5Is). However, these options are often only partly effective, begging the need for more dependable interventions.

Animal models that can physiologically mimic cavernous nerve (CN) injury have an important role in the advancement of the field and improved quality of life for these patients. The rat model has become a standard research method because of relatively lower costs compared with larger-animal options. Furthermore, the CN in the rat is a distinct entity that clearly branches off the major pelvic ganglion (MPG) on the dorsolateral aspect of the prostate.[3,4] In contrast, the CNs of humans are part of a neurovascular bundle, which is difficult to isolate and dissect, making it susceptible to damage during pelvic surgery. During radical prostatectomy, inadvertent injury from stretching, thermal injury, and crushing can initiate neurodegeneration.[3,5,6] The lack of innervation to the corpus cavernosa can lead to irreversible downstream damage to the erectile tissue from fibrosis and damage to blood vessels.[7]

In the rat model, crush injury, cautery, freeze injury, transection, and excision have been used to mimic possible

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damage that occurs during the radical prostatectomy procedure.[5] A comparison of groups, institutions, and techniques for the crush injury model has seldom been discussed. Furthermore, unilateral CN injury can result in compensation from the contralateral, uninjured nerve. Therefore, this comparative review focused specifically on the injury that occurs with bilateral crush injury.

METHODS

Data Collection

A literature review was performed on January 1, 2017 on PubMed (www.ncbi.nlm.nih.gov) using the search strings *cavernous nerve* and *injury* and *erectile dysfunction* and *rat*. This search yielded 114 original research articles. The search was restricted to the rat animal model and the bilateral CN crush injury (BCNI). Investigators had to have used electrostimulation to obtain the parameter of the ratio of maximum intracavernous pressure (ICP) to mean arterial pressure (MAP). All articles using unilateral crush injury, transection, excision, cautery, or freezing methods were excluded. Studies that did not report voltages or stimulated voltages no higher than 1 V were excluded. All articles with results that did not normalize to MAP were excluded. There were many articles that reported data graphically, but not numerically. These studies were included in the summary tables with an approximation, but without an estimate of the SD. In articles with multiple therapeutic interventions or doses, only the therapy with the highest efficacy was included in the summary tables. Acute studies, in which intracavernosal or intravenous injection therapy was used at the time of stimulation, were excluded.

In addition, all studies involving stem cells were excluded from this study, because a systematic review and meta-analysis was performed by Shan et al.[8] Studies included were grouped into five main categories based on their pharmacologic interventions: immune modulation, growth factor therapy, receptor kinase inhibition, PDE5I therapy, and antifibrotic and anti-inflammatory therapy. Studies that did not fit these categories were excluded.

After exclusion, 15 articles were included in the summary tables for maximum ICP/MAP. In 11 articles, data were estimated from bar graphs. In the summary tables, these numbers are preceded by an approximation sign. Next, the end points of the articles with full data were analyzed in a meta-analysis. Data were collected on sham, crush, and therapy groups, time of end point, number of rats, maximum ICP/MAP with standard errors or SDs, and voltage. Percentage of injury was calculated by comparing crush values with the corresponding sham values. Percentage of therapeutic resolution was calculated by comparing the therapy groups with crush-injured groups. For articles with missing SDs, SDs were calculated from standard error, mean, and number of rats.

Statistical Analysis

Statistical analyses were performed using STATA 12.1 (StataCorp LLC, College Station, TX, USA). Fixed-effect meta-analysis models with crush time, voltage used, and end-point weeks were used to assess the heterogeneity within each subgroup. Because of the high heterogeneity within each subgroup, a meta-regression was done using difference in ICP/MAP between sham and control rats as the dependent variable. The independent variables were crush time, voltage, and end-point weeks. For crush time, articles were divided into two groups: shorter than 120 seconds and equal to or longer than 120 seconds. For voltage used, the values were divided into voltage lower than 7.5 V and equal to or higher than 7.5 V. For end-point week, the values were divided into shorter than 2 weeks and equal to or longer than 2 weeks. A P value less than .05 was considered statistically significant.

RESULTS

Literature Summary and Comparison Tables

Immune Modulation.

Articles on immune modulation are presented in Table 1. There were two articles that met the inclusion criteria and used various interventions to affect the immune response to nerve injury. Immunosuppressive drugs used after donor organ

Table 1. Immunotherapy

					ICP/MAP results		
Study	Agent	Crush	Stimulation	End point	Sham	Crush (% Injury)	Therapy (% Improvement)
Canguven[6]	FK506 or rapamycin	Ultrafine hemostat, 3 min	16 Hz, 4 V, 50 s	day 1	~0.60	~0.30 (50%)	~0.55 (83%)
				1 wk	~0.65	~0.25 (62%)	~0.45 (80%)
Mulhall[21]	FK506	Dumont #7 hemostat, 30 s, 2×	20 Hz, 7.5 V, 60 s	day 3	0.70 ± 0.06	0.18 ± 0.10 (74%)	0.32 ± 0.03 (78%)
				day 10	0.70 ± 0.06	0.31 ± 0.13 (56%)	0.30 ± 0.17 (−3%)
				4 wk	0.70 ± 0.06	0.32 ± 0.08 (54%)	0.50 ± 0.09 (56%)

ICP = intracavernous pressure; MAP = mean arterial pressure.