



Estrogen Nanoparticles in Spinal Cord Injury

April Cox (1); Naren Banik (1) (3); Alexey Vertegel (2); John Barry (2); Abhay Varma MD (1)

(1) Medical University of South Carolina, Department of Neurosurgery

(2) Clemson University, Department of Bioengineering

(3) Ralph H. Johnson VAMC, Charleston SC

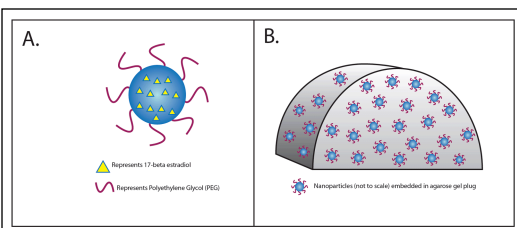


Introduction

Safe and effective treatment of acute spinal cord injury (SCI) is in urgent need. Estrogen is a promising neuroprotective agent with anti-inflammatory, anti-oxidant, anti-apoptotic, angiogenic, and neurotrophic properties. Systemic administration of high dose estrogen can be associated with serious adverse effects like venous thrombosis, however. Advances in nanomedicine have allowed for smarter drug delivery systems, providing novel alternatives to traditional dose routes. Nanoparticles loaded with estrogen may allow for focal estrogen delivery to the spinal cord with a maximal therapeutic response while sparing adverse effects.

Methods

Estrogen (17-Beta estradiol) was formulated into PLGA polymeric micelle nanoparticles and embedded into 0.6% agarose gel plugs. In the rat SCI model a gel plug embedded with estrogen containing nanoparticles was applied directly to the lesion within 5 min following injury. Animals were sacrificed at 48hrs post injury. Estrogen ELISAs were used to determine estrogen levels from rat plasma. Western blots were performed on lesioned tissue at 48hrs to evaluate markers of inflammation, apoptosis, and neurotrophin expression.

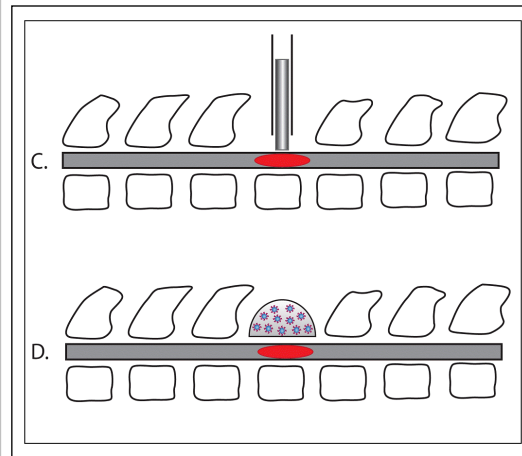


A. PLGA nanoparticle loaded with estrogen B. nanoparticles in agarose gel plug

Methods: Schematic of Estrogen Nanoparticle Delivery

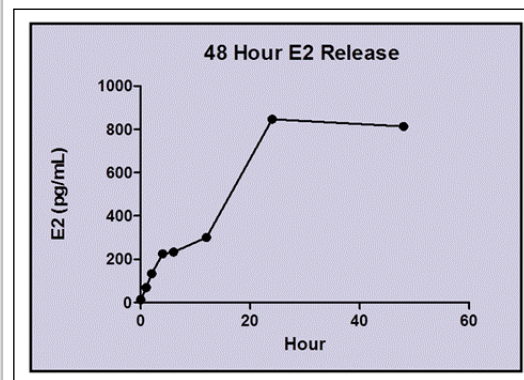
C. Moderate / severe contusion injury performed at T9/10

D. Placement of agarose gel plugs directly onto lesion site



Results

Figure 1.

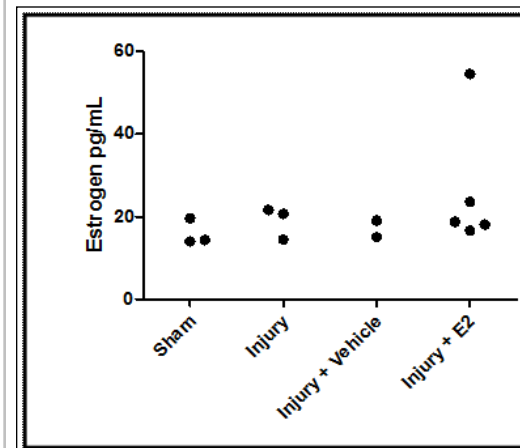


Estrogen released from nanoparticle embedded gel plug into cell culture media. Media was serially sampled and analyzed for Estrogen concentration. Data show release of estrogen into media over 48hrs.

Results

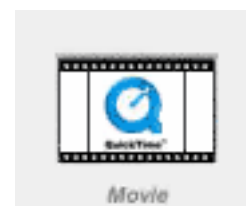
Figure 2.

Estrogen Plasma Concentration



Estrogen delivered via nanoparticle embedded gel plugs shows comparable plasma levels to non-treated animals at 48hrs following application.

Figure 3.



Western Blots at 48hrs following Estrogen Treatment

Conclusions

1. Estrogen nanoparticles can successfully deliver estrogen to contused spinal cord via agarose gel plug delivery system
2. In 48hr rat model of SCI Estrogen treatment resulted in decreased COX2, glutamine synthase, BAX/BCL2 expression, and increased GDNF expression indicating potential for therapeutic effects.

In conclusion, estrogen loaded nanoparticles may provide a safe and effective drug delivery approach in the treatment of spinal cord injury.

Learning Objectives

1. Evaluate the neuroprotective potential of targeted delivery of estrogen loaded nanoparticles in a preclinical model of acute SCI

2. Evaluate pharmacokinetics of estrogen loaded nanoparticle gel delivery

Acknowledgements

Clemson Bioengineering Department for supplying the nanoparticles. Funding from the Ralph H. Johnson VAMC, SCRIF, NIH, and Dept of Neurosurgery