Steroid-loaded Hemostatic Nanoparticles Alleviate Injury Progression after Blast Trauma

W. Brad Hubbard[1], Margaret Lashof-Sullivan[2], C. Shaylen Hall[1], Erin Lavik[2], Pamela J. VandeVord[1,3]

[1]School of Biomedical Engineering and Sciences, Virginia Tech University, Blacksburg, VA
[2]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
[3]Research Services, Salem VAMC, Salem, VA

Abstract

The purpose of this study was to investigate whether hemostatic dexamethasone-loaded nanoparticles (hDNP) functionalized with a peptide that binds with activated platelets could reduce cellular injury and improve functional outcomes in a model of blast trauma. Functionalized nanoparticles, or synthetic platelets, offer a wide variety of benefits and advantages compared to alternatives, such as increased biocompatibility and targeting of the injury site (DePalma, 2005). Blood loss is the primary cause of death at acute time points post injury in both civilian and battlefield traumas. Currently, there is a shortage in treatments for internal bleeding, especially for rapid administration in open field combat. In a recent U.K. study, less than fifty percent of soldiers diagnosed with primary blast lung injury (PBLI), the most common fatal blast injury, survived to reach a medical facility (Smith, 2011). This study examines potential therapeutic effects of hDNP on subacute recovery in brain pathology and behavior after blast polytrauma.

An established polytrauma model that simulates severe injury, including PBLI and blast-induced neurotrauma (BINT), can be used to evaluate life-saving therapeutics (Hubbard, 2014). Poly(lactic-co-glycolic acid)-based nanoparticles with poly(ethylene glycol) arms and the arginine-glycine-aspartic acid (RGD) peptide to target activated platelets were fabricated. A blast-induced polytrauma rodent model was used to evaluate the functionalized nanoparticles at an acute stage. After anesthesia, Male Sprague Dawley rats were exposed to a single, representative "free field" blast wave from an Advanced Blast Simulator at Virginia Tech at a peak overpressure of 28 psi for 2.5 ms duration, operating above 50% lethality risk, in a side-thorax orientation (Hubbard, 2014). After injury, animals were immediately injected intravenously with hDNP, control dexamethasone-loaded nanoparticles (cDNP), or lactated ringers (LR) and physiological parameters were monitored. Sham animals were not injected or exposed to the blast wave. Open field assays were performed on surviving animals to measure levels of anxiety. At one week post-blast, brains were extracted and sections from the amygdala were obtained for immunofluorescent staining using glial fibrillary acidic protein (GFAP; activated astrocytes), cleaved caspase-3 (apoptosis), and SMI-71 (blood-brain barrier).

According to physiological monitoring immediately after blast, oxygen saturation was significantly decreased in the control and LR groups compared to the active and sham groups. Using the open field test, elevated anxiety parameters were found in the control and LR groups compared to the hDNP group. GFAP was significantly elevated in the control group compared to the hDNP and sham groups in the amygdala. Caspase-3 was also significantly elevated in the control group compared to the hDNP group. SMI-71 was significantly reduced in the LR group compared to the sham group.

hDNP treatment has the potential to assist recovery after internal hemorrhage. Immediate intervention to assuage hemorrhage, one source for injury pathology, is crucial to mitigate debilitating injury mechanisms that lead to cognitive and emotional deficits (Shetty, 2014). It is possible that through prevention of microhemorrhaging of the blood-brain barrier (BBB), hDNP was able to mitigate cellular injury and improve cognitive outcomes. Future studies will evaluate the effect on inflammatory and hypoxia-related proteins after hDNP administration post-trauma.