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Targeting Delivery of Dexamethasone Ameliorates Post Traumatic Brain Injury Neuroinflammation and Prevents Bone Loss in the Murine Model

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Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in children and adults. The pathology of TBI is heterogeneous, resulting from both primary and secondary injury mechanisms, the latter being attributed to the inflammatory response. The long-term neuronal inflammation and neurodegeneration impairs patients' memory, emotions, balance and cause sensory and motor weakness. Glucocorticoid was reported dose-dependent effective for the treatment of neuroinflammation post-TBI. The use of conventional glucocorticoid formulations (e.g., dexamethasone or Dex) leads to limited distribution to the brain, pulsatile brain tissue concentration and systemic side effects, with controversial benefit in being neuroprotective. We hypothesized that systemically administered a N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-based Dex prodrug (P-Dex) will target the brain trauma injury sites, provide sustained controlled release of Dex, substantially enhance the therapy efficacy, and improve its systemic safety. Mice (C57BL/6, 9 weeks old, female) were randomly assigned to P-Dex, Dex, saline and healthy control groups (n=15). After establishment of the TBI (cortical impact), mice received the respective treatments and control via injection. They then underwent neurological severity score, static weight bearing test. The collected brain tissues were evaluated using optical imaging and immunohistochemistry. The bone quality was assessed using micro-CT. We found that P-Dex passively targeted the traumatic brain tissue and had sustained accumulation at the inflamed tissue for over 14 days. Histological evidence demonstrates the P-Dex's therapeutic effect on the amelioration of neuroinflammation and prevention of neurodegeneration. Behaviorally, the P-Dex treated animals showed better recovery of the imbalance. Higher bone mineral density and better bone microarchitecture were evident in the P-Dex treated animals, comparing to the free Dex treated animals, and Saline control, confirming the P-Dex's bone protection effect. P-Dex can be a potential therapy targeting neuro-inflammation and preserving the neurons from death, avoiding bone loss post-TBI preventing growth retardation in the pediatric patients.