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Liver Trauma: An Insight into Therapeutic Approach

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Abstract

Liver injury has been a major problem for a few decades. There is a burgeoning need to develop appropriate armamentarium to overcome liver injury in specific and abdominal injury in general. Recently, nanotechnology approach has been gaining grounds to treat multifarious gastrointestinal disorders. A few therapeutic avenues are discussed in this review, which entail the design, characterization and applications of therapeutic hydrogels.

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Introduction

Liver is the most commonly injured internal organ in abdominal injuries although well protected behind the sub costal region[1]. Epidemiological studies revealed that death rate is significantly high in penetrating trauma patients compared to blunt trauma patients[2]. With a view to understanding the severity of liver trauma blood transfusion has been considered as an index of mortality and hospitalization status in patients with blunt liver and spleen injuries. Enhanced transfusion-associated mortality risk in non operative patients indicates the substantial need to reconsider and ameliorate current transfusion practices[3]. Despite the multifarious advantages of non-operative management in the treatment of liver trauma a few patients with high Injury Severity Score (ISS) require operational management.

Multifarious treatment options to overcome liver trauma include but not limited to hepatic artery embolization[4], absorbable mesh wrapping, use of bioglue, liver transplantation[4], and employment of hydrogels. In this review, a few studies which employed nanoparticles to overcome liver injury have been discussed.

Therapeutic Avenues for Livery Trauma

Diagnosing the extent of liver trauma and understanding the severity play a key role in employing appropriate treatment strategies. Patients with severe hepatic trauma involving hemodynamic instability require surgical intervention. Novel therapeutic avenues such as hepatic artery embolization and liver transplantation have been extensively used in the treatment of extremely severe hepatic damage currently[4]. Although angioembolization procedure shows the success rate of 93%, a few associated complications such as hepatic necrosis (15%), abscess formation (7.5%), and bile leaks limit its success[5]. In another study, studies on wistar rats showed that the collagen adhesive associated with fibrinogen and thrombin successfully attenuates experimental hepatic injury by curtailing the occurrence of adhesions between the liver and the surrounding structures[6]. Recently, *in vitro* and *in vivo* studies showed that betaine which is an ingredient in food and also synthesized in liver, plays a pivotal role in reversing the liver injury significantly[7].

Absorbable mesh-wrapping has been used to overcome the liver trauma[8]. Remarkably reduced incidence of septic complications and absence of re-bleeding hazard are a few advantages associated with this treatment. Growing lines of evidence sug-

gests that application of Cryo Life Bioglue also effectively seals the laceration and improves the repair process[9]. Bai, et al.[10] designed genetically engineered cells harboring the theranostic gene circuits which provoke therapeutic protein production in response to the increased bile content due to the liver injury. In order to circumvent the issues associated with the above mentioned therapies, nanotechnology has been employed to design potential particles.

Nanotechnology to Overcome Liver Injury

Superparamagnetic iron oxide-coated gold nanoparticles (SPIO@AuNPs) targeted against liver injury showed appreciable therapeutic efficacy in mice[11]. To prepare these nanoparticles amorphous silica coated SPIO nanoparticles were reacted with 2 - 3 nm gold nanocrystals. The obtained particles were centrifuged and rinsed with deionized water. These nanoparticles transfected into adipose-derived mesenchymal cells showed enhanced theranostic efficacy. They were administered into mice in which liver damage was induced by 2-acetylaminofluorene. The *in vivo* non-invasive MR imaging was achieved by these nanoparticles. In line with this, these nanoparticles can be an appropriate theranostic armamentarium for livery injury.

Hydrogels

Hydrogels play a pivotal role in sustained drug release, tissue engineering matrices since they closely resemble extracellular matrix. The synthesis, characterization and applications of hydrogels have been thoroughly reviewed[12-14]. Since the robust discovery of Hydroxyethyl Methacrylate (HEMA) hydrogels in 1960, they have been extensively utilized for biomedical applications[15]. Multifarious hydrogels currently in use for a wide range of diseases include but not limited to stimuli sensitive hydrogels[16-29], redox-active injectable hydrogels[30-34].

Wealth of studies showed that the traumatic hemorrhage can be successfully overcome by employing multifarious hydrogels[35]. Horio et al., developed photocrosslinkable chitosan hydrogel to accomplish hemostatic efficacy and treat liver injury[36].

Studies on keratin hydrogels unraveled that liver injury can be successfully overcome. In this study, keratin isolated from hair was flocculated with Phosphate Buffered Saline (PBS) and citrate buffer and incubated at 37°C for 12 hours. Further it was centrifuged and keratin pellet was washed with PBS or Dulbecco's Modified Eagle Medium (DMEM). With a view to developing fibroblast encapsulation flocculated keratin solution and cell culture medium were mixed followed by addition of cell suspension. Cell loaded hydrogels were incubated at 37°C and 5% CO_2 for 8 hours and culture medium was added. *In vitro* L929 culture studies showed that cell viability was appropriate during encapsulation and a 16 day culture period. The remarkable *in vivo* retention of these hydrogels and significant less contraction compared to collagen hydrogels make them a substantial platform to overcome liver injury[37-40]. The success of these hydrogels offers a significant impetus to the drug candidate screening research. In another study, keratin based hydrogel with the self assembly property showed better interaction with cells and enhanced therapeutic effect[41]. Furthermore, in a recent study hepatic growth factor loaded hydrogel showed specific therapeutic efficacy against acute hepatic failure. In this study, functional induced pluripotent stem cells (iPSC-Heps) were designed by reprogramming human dental pulp fibroblasts. Further, an injectable Carboxymethyl-Hexanoyl Chitosan (CHC) nanoscale hydrogel with controlled release of Hepatocyte Growth Factor (HGF) (HGF–CHC) was synthesized, and the growth capacity and hepatic-like functions were evaluated. Eventually, hepatoprotective efficacy of HGF-CHC transplanted with iPSC-Heps was targeted in Thioacetamide (TAA)-induced AHF *in vivo* model. Significant therapeutic efficacy of the designed material has been observed[42]. While a few key issues limited the success of hydrogels until recently, novel hydrogels that were designed and used in 3D cell culture systems showed significant efficacy in protecting the liver enzymatic activities. Despite the advent of advanced therapeutic armamentarium, treatment of liver trauma remained a herculean task till date.

Conclusion

Hepatic trauma is the most common in abdominal injuries and reposes a serious threat to the life of patients. Although non-operative treatment for liver trauma has been extensively used yet operative treatment is essential in severe cases. Despite the availability of multifarious therapeutic avenues such as bioglue, mesh-wrapping, hydrogels, lack of appropriate armamentarium is an Achilles heel till date. A multidimensional approach involving the theranostic strategy such as gene circuits may be a promising therapeutic option to overcome these liver and associated abdominal traumas. Therefore, there is a burgeoning need to develop a substantial therapeutic arsenal by utilizing the panoply of available data.

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