Genipin Crosslinker Releasing Sutures For Improving The Mechanical/Repair Strength Of Damaged Connective Tissue

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Introduction: The most common mode of surgical repair of ruptured tendons and ligaments involves the use of sutures for reattachment (1). However, there is high incidence of re-rupture and failure of repair due to pulling out of the suture material from the recovering connective tissue (2). The main goal of this research is to achieve a localized delivery of crosslinking agent genipin (GP) from rapid-release biodegradable coatings on sutures, for strengthening the repair of ruptured connective tissue (3). Our hypothesis is that GP released from the suture coating will lead to exogenous crosslinking of native connective tissue resulting in beneficial effects on clinically relevant mechanical parameters such as tear resistance, tissue strength, and energy required to rupture the repaired tissue construct (toughness).

Methods: Prototypes were fabricated by coating poly glycolic acid (PGA) sutures with a poly lactic-co-glycolic acid (PLGA) layer containing GP. The coating formulation consisted of PLGA and GP dissolved in a co-solvent system of acetone and dimethyl sulfoxide (DMSO). A plasticizing agent, poly ethylene glycol (PEG), was also added to the formulation to retain the flexibility of the coated sutures. Sutures were dip coated and dried for the evaporation of the solvent. The amount of GP loaded in the suture coating was determined by high performance liquid chromatography (HPLC) and the tensile strength of the coated sutures was compared with that of the control sutures. Suture segments 1 cm in length were incubated in a glycine solution (0.75 mg/ml, 37 °C) to analyze the release profile of genipin from the coating. At specific time intervals the suture segments were removed from the glycine solution and re-dissolved in acetone. The acetone solution was analyzed using HPLC to determine the amount of GP remaining in the suture coating at different time points. The coated and control sutures were used in the form of a Kessler knot (one of the most commonly used knots for tendon repair) in equine deep digital flexor tendons, and the mechanical properties of the construct such as load to failure, toughness and stiffness were studied.

Results: The stiffness and load to failure determined from the tensile testing of coated and non-coated sutures showed no meaningful or statistically significant difference (Figure 1).

![Figure 1: Failure load (A) and stiffness (B) of control and coated sutures obtained by tensile testing. Data are mean ± SD, n=6.](image-url)
The release profile obtained (not shown) showed the typical bi-phasic release pattern that is observed in a PLGA delivery system. The initial burst in the release is mainly due to the diffusion of GP from the coating, accounting for more than 60% of the agent being released in the first few minutes. This was followed by the gradual release of the remaining GP as the PLGA matrix which formed the coating degraded over the next 12 hours.

Images showing tendons sutured with control and genipin loaded sutures using Kessler knots can be seen in Figure 2. The blue color is a by-product of crosslinking indicating that genipin had been released from the sutures and diffused into the tissue. Both the control samples and the treated samples were loaded to failure by suture pullout, and the load at failure, toughness and stiffness of the samples were calculated (Figure 3).

![Image of tendons](image)

**Figure 2: Tendons sutured with control (Right) and genipin loaded sutures (Left).**

The results show that the toughness, failure load and stiffness of the treated tendon increased by 135% (p=0.007), 67% (p=0.012) and 21% (p=0.003) respectively, compared to the control tendon (Figure 3). This preliminary study consisted of 4 controls and 4 treated tendons, and the results obtained were statistically significant. Figure 3 shows the comparison of the load-displacement curves of a representative control tendon and treated tendon.
Discussion: In conclusion, the results of this study showed that pull out tests of genipin-releasing coated sutures from tendons showed significantly higher load to failure, toughness, and stiffness than non-coated sutures without negatively affecting the mechanical properties of the suture itself. This confirms that the GP released from the suture coating is successful in crosslinking the collagenous tissue and increasing the resistance to pull out of the suture by improving the mechanical strength of the construct.

Significance: Repair of connective tissue primarily involves the use of sutures and has a high incidence of re-rupture and failure due to pulling out of the suture material from the recovering tissue. The results of this study show that a genipin-loaded coating applied to currently used suture materials can lead to increased resistance to pull out.

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