AB085. E-beam sterilization of recombinant human collagen-phosphorylcholine corneal implants for transplantation

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Background: The sterilization of corneal implants composed of carbodiimide crosslinked recombinant human collagen type III (RHCIII) and phosphorylcholine polymers (RHCIII-MPC) is constrained by the biochemical properties of RHCIII. Early human trials used 1% chloroform in 0.1 M phosphate buffered saline (C-PBS), but require a stringent wash procedure with antibiotics to remove the chloroform. Irradiation with gamma or electron-beam (e-beam) allows a chemical-free sterilization method, but may result in crosslinking or denaturation. Here, electron-beam irradiation is evaluated as a sterilization method for RHCIII-MPC implants.

Methods: Dose-finding study: RHCIII-MPC were cast in round, 350 µm thick, 12 mm diameter molds for corneal implants and 0.5 mm thick dumbbell-shaped molds for mechanical testing. The hydrogels received an irradiation dose of 17, 19, or 21 kGy and unirradiated controls were stored in C-PBS, n=3 per group. The hydrogels were tested for sterility and endotoxin, optical and mechanical properties, biodegradation, free radicals, and cell compatibility. Clinical evaluation in rabbits: RHCIII-MPC implants were e-beamed at 17 kGy or kept in C-PBS. One implant from each group was implanted into the right cornea of each rabbit by deep anterior lamellar keratoplasty, n=4 animals per group. Animals underwent preoperative and 6-month post-operative *in vivo* confocal microscopy (IVCM) to check nerve count and ingrowth of keratocytes. Corneal grafts and controls were assessed via histology and immunohistochemistry.

Results: Dose finding study: hydrogels were sterile at all irradiation doses with no evidence of free radicals. There were no significant differences in optical or mechanical properties between the treatment groups and controls. All hydrogels supported cell growth. The 19 and 21 kGy implants had high collagenase degradation for 21 hours until they stabilized, whereas the 17 kGy and C-PBS implants had gradual degradation until 48 hours. Clinical results: the rabbits did not experience post-surgical inflammatory reactions and full epithelial coverage of the implants occurred within the first week of surgery for all animals. Mild neovascularization occurred in all animals, but resolved by 6-month follow-up. A mild 0.5–1.0 grade subepithelial haze was observed in all rabbits, but the implanted grafts remained transparent. Re-innervation occurred in all grafts with no significant differences between sterilization methods. All regenerated corneas had mucin production and were positive for cytokeratin 3 and 12. Grafted and control corneas were negative for macrophages and blood vessels.

Conclusions: E-beam sterilization is a safe and effective form of sterilization for RHCIII-MPC implants.

Keywords: Cornea; collagen; tissue scaffolds; implant; regenerative medicine

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