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Sustained-Release 9-cis Retinoic Acid Pellets for the Prevention of Postsurgical Lymphedema
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Purpose: Lymphedema is a disfiguring disease affecting over 250 million people worldwide. Nine-cis retinoic acid (9-cis RA) has recently been shown to limit postsurgical lymphedema and is already approved for clinical use in the US and UK for other conditions. Previous animal studies have tested 9-cis RA in intraperitoneal injection form, which has poor translatability to future clinical trials. The purpose of this study is to investigate the pro-lymphangiogenic effects of 9-cis RA contained within a single-use depot pellet drug delivery system in a clinically relevant mouse lymphedema model.

Methods: Hindlimb lymphedema was induced in 18 mice via combined lymphatic injury, consisting of inguinal and popliteal lymphadenectomy followed by irradiation. Animals were split into 2 groups: 1) the treatment group received pellets containing 9-cis RA, 2) the control group received placebo pellets. Pellets were placed within the surgical wound intraoperatively, with experimental pellets resulting in sustained drug release. Paw thickness was measured weekly for 6 weeks and normalized by calculating percent change relative to the unaffected paw. Lymphatic drainage was measured at postoperative week 6 via indocyanine green (ICG) lymphography.

Results: Compared to control animals, significantly less paw swelling was observed in 9-cis RA-treated animals at postoperative weeks 3 (7% change, P<0.05), 4 (12% change, P<0.001), 5 (9% change, P<0.001), and 6 (11% change, P<0.001). No significant difference in paw thickness was observed within the treatment group over time, indicating reduced lymphedema progression. 9-cis RA-treated animals had significantly faster lymphatic drainage than control animals as measured by ICG clearance (P<0.05).

Conclusion: Animals treated with 9-cis RA pellets at the time of surgery demonstrate significantly less paw swelling the first 6 weeks after lymphatic injury and faster lymphatic drainage compared to control animals. In conclusion, we demonstrate that single-use 9-cis RA pellets have favorable properties in limiting postsurgical lymphedema.