Click Chemistry Hydrogel Effectively Delivers Vancomycin in a Rat Surgical Site Infection Model

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INTRODUCTION: Surgical site infections (SSIs) are a major post-operative complication, leading to increased morbidity, mortality, and healthcare costs for patients, particularly in orthopaedic surgical procedures. Current systemic antibiotic therapies, including vancomycin for *Staphylococcus aureus* (MSSA and MRSA), are not very effective since they exhibit rapid clearance from circulation and poor penetration into deep musculoskeletal tissues. While vancomycin powder is often applied intraoperatively, there are no FDA-approved biodegradable materials that provide localized, sustained antibiotic release directly to the surgical site. To address this, we have developed ClickGel, an injectable, biodegradable polyethylene glycol (PEG)-based Cu++-free click chemistry hydrogel that rapidly polymerizes in situ, and allows sustained therapeutic delivery. The purpose of this study was to evaluate the effectiveness of ClickGel for preventing SSI due to MRSA.

METHODS: **In Vitro Studie**s- QuickGel's antibiotic release kinetics were quantified via spectrofluorometric measurement of vancomycin concentration over fourteen days. The antibacterial effect of ClickGel's antibiotic release profile was assessed using a Kirby-Bauer disc inhibition assay against Methicillin-Sensitive Staphylococcus aureus (MSSA) and Methicillin-Resistant Staphylococcus aureus (MRSA). **In Vivo Studies**- A rat muscle pouch model was used to simulate SSIs. Groups included Sham (n=4), ClickGel (n=4), MRSA (n=6), MRSA+Powdered Vancomycin (n=6), and MRSA+Vancomycin+QuickGel (n=6). Two cohorts of 250g male Sprague Dawley rats were evaluated; one cohort evaluated tissue homogenate and subsequent bacterial culture, and one cohort evaluated bacterial load histologically using Brown Hopps Gram-stained and haematoxylin and eosin-stained tissue sections from the muscle pouches. Multiple fields of view were analyzed per section from each sample, and the results were evaluated by an independent veterinary pathologist. Non-target tissue histology was performed on the lungs, liver, kidneys, and spleen of sham and ClickGel-treated rats to assess the systemic effects. 2 × 10^7 CFU MRSA were applied per pouch, and confirmed by retrospective plating and infection progression over 14 days. A standard dose for Vancomycin in rats is 20mg/kg. Therefore, 5mg of powdered Vancomycin, or 300µL of ClickGel containing 5mg of Vancomycin, was implanted in the muscle pouch. The Institutional Animal Care and Use Committee of George Mason University approved the study. Female animals were not evaluated in this study; however, future work will include a replication of this study in female animals.

RESULTS: ClickGel released approximately 20% of the Vancomycin load over fourteen days in vitro. Antibiotic released from the ClickGel was able to achieve significant inhibition zones versus both MSSA and MRSA bacteria. The addition of ClickGel in the muscle pouch had no adverse effect. Culture results, as measured by CFU of the thigh homogenate from the five experimental groups after fourteen days, showed significantly fewer bacteria in the MRSA+ClickGel+Vancomycin group compared to the MRSA alone group, while no difference was observed in the MRSA+Powdered Vancomycin group (Figure 1A). Histologically, Gram-positive bacteria were found in 6/6 MRSA samples, 4/6 MRSA+Powdered Vancomycin group, and 1/6 samples in the MRSA+ClickGel+Vancomycin group (Figure 1B). Non-target tissue histology (lung, liver, spleen) showed no adverse effect of the ClickGel, including inflammation or necrosis.

DISCUSSION: The method of antibiotic delivery impacts the bacterial load in a surgical site infection model. ClickGel sustainably released an effective amount of Vancomycin over fourteen days in vitro. The localized, sustained release of Vancomycin from ClickGel yielded a significantly reduced bacterial load compared to the bacterial control, whereas the standard of care, powdered Vancomycin packed into the site, did not show a significant difference. This was confirmed histologically in a completely separate animal cohort. ClickGel effectively delivers and sustains antibiotic levels at surgical sites for up to fourteen days, offering a novel solution to SSI prevention. Its injectable, space-filling properties allow seamless integration into complex wound environments.

SIGNIFICANCE/CLINICAL RELEVANCE: Surgical site infections are very prevalent in orthopaedic procedures. Systemic delivery of antibiotics is less than desirable, often producing unwanted effects in patients, and may require lengthy hospital stays to administer them, resulting in an increased burden on both the patient and the healthcare system. The present study demonstrates that localized, sustained prophylactic antibiotic delivery at the time of surgery can significantly reduce the prevalence of surgical site infections and enhance the healing.

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Figure 1:

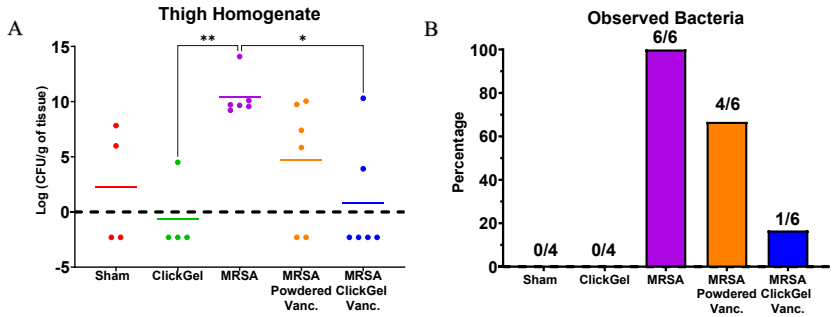

Figure 1: A) Culture results reported as CFU/g of tissue following homogenization of the muscle pouch. B) The percentage of observed bacteria following scoring of multiple fields of view of the complete gram-stained tissue section, as determined by an independent veterinary pathologist.