POSTOPERATIVE SPINAL INFECTION PREVENTION WITH GENTAMICIN-MICROSPHERES

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Introduction
Postoperative spinal wound infections occur at a rate of 1-5% in the non-compromised patient population undergoing elective posterior thoracolumbar spine surgery. Due to numerous systemic and local factors, the incidence of infection with predominantly *Staphylococcus aureus* in the traumatized spine occurs at 6-12%.(1) Multiple revisions for irrigation and debridements as well as the need for long term intravenous antibiotics lead to significant morbidity for the patient and pressures healthcare facilities with tremendous costs. Local hematoma harboring bacteria at the end of a procedure, combined with systemic malnutrition, tissue hypoxia and compromised skin while a trauma patient is supine in a hospital bed are important factors for this increased risk of infection.

Methods
We developed a reliable, controlled release delivery system for gentamicin to wounds and hematoma using PLGA resorbable microspheres (6-25 micrometers, resorption in 3-7 days) and tested this system using a well published non-contiguous spinal infection model in 40 New Zealand White rabbits.(2) The spheres were created from a mixture to contain a reliable 20% w/w gentamicin/PLGA and the Thomas Jefferson University IACUC approved all studies described in this investigation.

After pharmacokinetics of the release were studied in-vitro and in-vivo and compared to powdered gentamicin delivery, three non-contiguous sites (two treatment sites and one control site) were created in the spine of each rabbit, and wounds were challenged with a clinical *S. aureus* (ATCC 25923) strain. After 7 days, postoperative wound infection was assessed using standard tissue sampling and bacterial quantification techniques (fascia, hematoma and bone) to test our hypothesis that both incidence as well as severity of postoperative spinal wound infection can be reduced using controlled, local delivery of gentamicin using microsphere technology.

Results
Local delivery of gentamicin-microspheres resulted in controlled bactericidal levels of 20ug/ml hematoma for a minimum of 48hrs, while powdered delivery of equal amounts of gentamicin (450microg/site) resulted in cytotoxic ‘burst’-levels in the local wound above 130microg/ml for the first 36hrs.(3) Systemic gentamicin levels were negligible throughout the study (<1ug/ml).

After establishing a reliable infection in 78% of all challenged control sites, gentamicin-microsphere treatment reduced incidence of infection by 50% (p<0.001 – Chi-square). Severity of infection was reduced compared to controls by 1.5log values (p=0.003 – paired T-test) in the sites that showed bacterial growth. All animals survived the procedure and no surgical complications occurred.

Discussion / Conclusion
Local delivery of antibiotics to wounds and hematomas in the spine is an intuitively attractive option to sterilize the local environment where intravenous antibiotic prophylaxis cannot reach (hypoxic, devitalized tissue and pooled hematoma lacking vascular flow). Powdered gentamicin-crystal delivery, however, leads to cytotoxic levels of aminoglycosides (>100ug/ml) which has been shown to compromise tissue and pooled hematoma lacking vascular flow). Local delivery of gentamicin-microsphere controlled delivery successfully reduced the incidence and severity of *S.aureus* postoperative spinal wound infection while bactericidal levels of gentamicin remained at 20ug/ml for a prolonged period of time. The release duration and amount of antibiotic can be regulated by sphere size, as well as antibiotic concentration in the PLGA mixture. Optimum antibiotic concentration for 3-5 days (quick on-off system) without prolonged delivery can both be effective, as well as low risk to induce antibiotic resistance as is the danger with PMMA-beads or equivalent delivery systems.

Clinical investigation in postoperative spine wounds in traumatized patients is being discussed to prove clinical efficacy and potentially allow this treatment to become the standard of care as an adjuvant in the high-risk patient population. Using the data from this study, a human efficacy trial that can possibly be performed to combat postoperative (implant associated) infection, since the current incidence of infection is so high in this specific patient population.

References

Figure 1: Local tissue levels of gentamicin after powdered- or microsphere controlled delivery to surgical wounds in the spine of New Zealand White rabbits (experiment performed in triplicate).

Figure 2: Representative clinical image after intra-operative *S.aureus* challenge (10^3CFU) of two adjacent spinal sites showing significant wound healing differences and bacterial numbers between a control- and gentamicin-microsphere treated site.

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